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From the Departments of Pathology (B. I.) and Pediatrics (R. Z.), Karolinska Sjukhuset, Stockholm, and the Department of Pediatrics (V. O.), Centrallasarettet, Linköping

Familial Dysplasia of Kidneys, Liver and Pancreas

A Probably Genetically Determined Syndrome

by BIÖRN I. IVEMARK, VERA OLDFELT and ROLF ZETTERSTRÖM

Various forms of renal dysplasia are known to occur in infancy and childhood. In one type the renal lesions may be one-sided or bilateral and in the more severe forms the kidney is underdeveloped and may contain many large cysts filled with clear fluid. Another type is the dwarfed kidney often associated with ureteral duplication where there is evidence of parenchymatous dysplasia (Ericsson & Ivemark 1958a and b). On the other hand, selective renal tubular dysplasia causing tubular dysfunction also exists, as is the case in the Fanconi syndrome (Fanconi; review by Piel). Hereditary dysplastic renal disease in association with another abnormality, such as nerve deafness, has also been reported (Goldbloom, Fraser, Waugh, Aronovitch & Wiglesworth). Furthermore, Faber has described the concomitant occurrence of congenital cirrhosis of the liver and renal tubular lesions reminiscent of those in the Fanconi syndrome.

The present study concerns two siblings who developed evidence of renal failure and who died in early infancy. At post-mortem examinations prominent renal dysplasia was found in association with

congenital abnormalities of the liver and pancreas.

Case reports

CASE 1.—A girl, the second child of healthy parents. There was no consanguinity and the family history was also non-contributory in other respects. Pregnancy and delivery were uneventful. Birthweight 3960 g. Vomiting started when the infant was one week old and after another week the patient was admitted to the Children's Hospital, Linköping, because of failure to thrive. Renal failure was diagnosed and the child was admitted to the Pediatric Clinic, Karolinska Sjukhuset, for urologic work-up.

On admission at an age of 6 weeks the infant looked very sick. She was dehydrated and wasted, the weight being 3300 g. There was a slight jaundice and the skin was rather pale. The cry was weak. There was no cyanosis or symptoms of respiratory distress. No abnormalities were found on the physical examination of the chest organs. The liver was enlarged and was palpated 4 cm below the costal margin, there was no splenomegaly. No lymphadenopathy was found.

There was a moderate normochromic anemia, the hemoglobin level was 7.9 g per 100 ml. The reticulocyte level was very high, 18 per cent. WBC 9400, the differential

count was normal. The mean red cell diameter was 7.2μ , and the erythrocytes had a normal resistance to hypotonic saline. The blood group was A, Rh(+) and the anti-globulin test of Coombs was negative. Wasserman reaction was negative.

Urinary examination showed a slight proteinuria, occasionally there was also a slight erythrocyturia. Some casts and white cells were also found in the urine. Specific gravity of the urine 1.008. The non-protein nitrogen level was 71 mg per 100 ml. The carbon dioxide combining power of serum was 25 mEq per l.

The phosphate concentration of serum was 9.6 mg per 100 ml and the calcium level was 10.4 mg per 100 ml. The alkaline phosphatase activity of serum was 30 Buch & Buch units. The serum bilirubin was 1.3 mg per 100 ml. The total serum protein level was normal (7.2 g per 100 ml, paper electrophoretic analysis showed a slight increase of the α_2 fraction, otherwise the pattern was normal).

Special investigations: Urologic examination disclosed no malformations in the urinary tract but urography showed a reduction of the concentration capacity. The kidneys were of normal size. There was no real evidence of pyelonephritis.

Treatment and course: Despite intravenous fluid treatment the infant remained dehydrated and there was no gain in weight. Vomiting persisted but the stools were normal. The slight jaundice which was present on admission disappeared. Despite blood transfusions the anemia persisted. There was a constant marked reticulocytosis. The serum alkaline phosphatase activity successively increased up to 59 units. Hepatomegaly persisted. Owing to renal failure there was a constant hyperazotemia; rather soon also marked hyperphosphatemia (18.8 mg per 100 ml) and hyperpotassemia (6.2 mEq per l) developed. Finally, the infant also showed evidence of acidosis, the carbon dioxide combining power of serum decreased to 10 mEq per l.

The infant expired at an age of 11 weeks

from symptoms suggesting acute cardiac failure.

The clinical diagnoses were chronic renal failure of unknown cause and hepatic insufficiency. The anemia, which was considered to be secondary to the renal disease, was thought to be mainly of hemolytic type.

The postmortem examination showed the body of a fairly well-nourished female, measuring 56 cm in length and weighing 4300 g. Pertinent gross findings: The lungs showed a small number of subpleural petechiae and small areas of atelectasis. The liver was greatly enlarged and showed a finely granulated surface, apparently corresponding to the lobular pattern. It was dark brown and firm. The extrahepatic bile ducts were normal. The pancreas was somewhat enlarged with grossly apparent lobulation and of increased consistency but without cysts. The pancreatic duct showed a normal opening in the duodenum. The portal vein and the inferior vena cava showed no abnormalities. The kidneys were small and weighed together 20 g. They were equally large, light brown and showed moderate fetal lobulation. The subcapsular surface was finely granular although the capsule was not adherent. The cortex was irregular and only slightly reduced in width. The corticomedullary junction was sharp, and in the medulla occasional yellow streaks were seen. The pelvis and ureters were normal on both sides. The urinary bladder was empty and normal.

Histologic examination of the kidneys revealed a condensed renal parenchyma with slight interstitial fibrosis and infiltrations of lymphocytes and plasma cells in small and large areas of the cortex. In addition to nonspecific changes there was evidence of dysplasia. In the medulla, the corticomedullary junction, and in the cortex, wide, occasionally cystic primitive tubules (Figs. 1-2) were found lined with cuboidal or cylindrical epithelium and surrounded by concentric connective tissue rings. The dysplastic changes occurred in a localized fashion in the cortex and medulla. No typical ductules as seen in renal dysplasia (Ericsson &

Fig.

Fig. 2.



Fig. 1. Case 1. Kidney. Low-power field showing abnormal primitive tubules in medulla and cortex. Hematoxylin-eosin, $\times 48$.

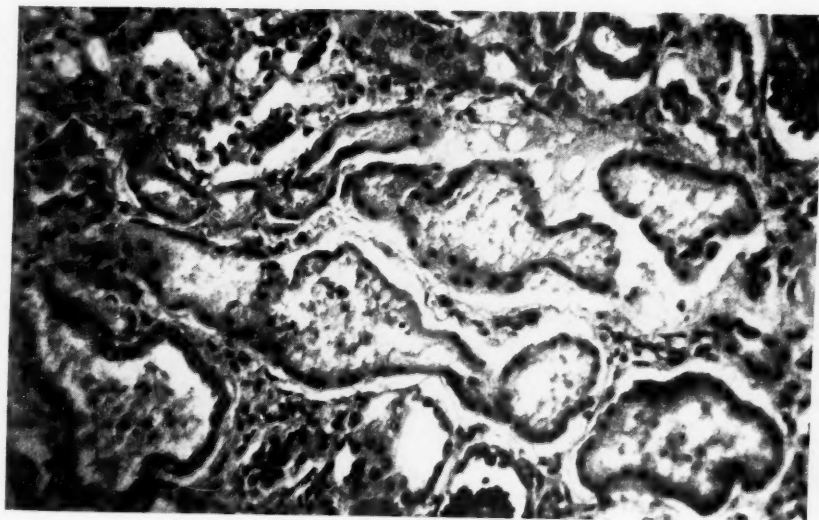


Fig. 2. Case 1. Kidney. Proximal convoluted tubule showing irregular dilatation. Interstitial edema. H & E, $\times 160$.

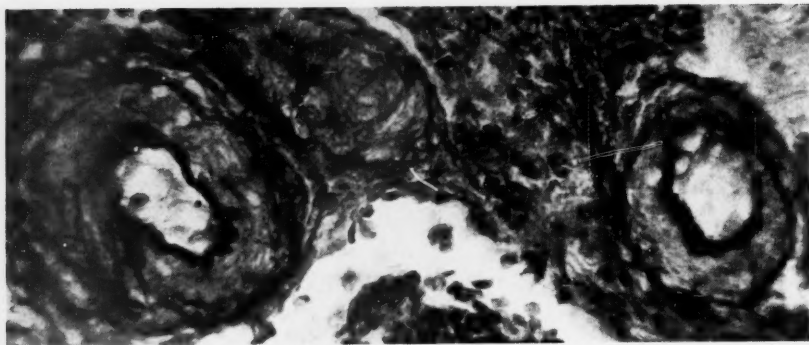


Fig. 3. Case 1. Kidney. Juxta-medullary arteries with irregular internal elastic laminae. Weigert's elastin. No counter-stain. $\times 320$.

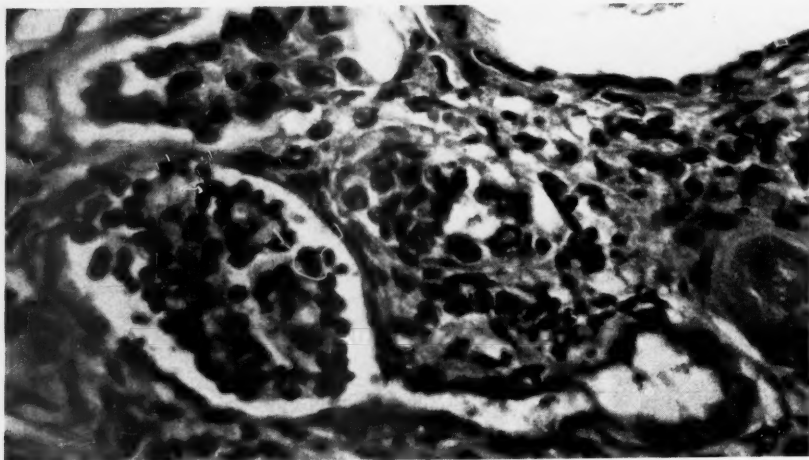


Fig. 4. Case 1. Kidney. Glomerulus joined by narrow tubular neck reminiscent of the swan-neck lesion. Note adjacent cyst. H & E. $\times 320$.

Ivemark, b) were present. There were no areas of cartilage or lymphoid tissue.

As is seen from Fig. 2 the abnormal dysplastic tubules found in the cortex were lined with a single layer of cylindrical epithelium. The nuclei were round with loose chromatin. In some cells subnuclear vacuoles were seen. There was no brush border. Outside the epithelium thin layers of concentric connective tissue rings were present, some tubules having embryonal character of loose reticu-

lar tissue. In the outermost layer a sparse amount of thin elastic fibers could be found. No definite smooth muscle was present. The lumens sometimes contained a small amount of proteinous fluid. Very few subcapsular tubules of similar structure were found.

The vasculature of the cortex was abundant and some of the vessels retained the rich fetal serous coat. In elastin-stained sections the internal elastic laminae were irregular (Fig. 3). The glomerular changes in-

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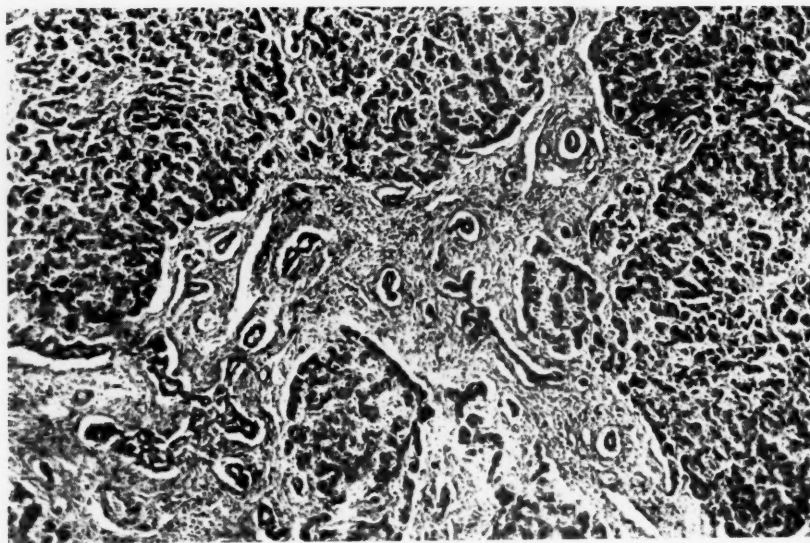


Fig. 5. Case 1. Liver. Portal tract with prominent embryonal connective tissue containing bile ducts. H. & E. $\times 48$.

cluded proliferation of the capsular endothelium resulting in more-or-less advanced fibrosis and hyalinosis. Some glomeruli were attached to tubules having the appearance of swan-necks (Fig. 4). These glomeruli were found adjacent to the abnormal primitive tubules described above. The proximal tubules were irregular and tortuous throughout (Fig. 2). The acidophilia of the cytoplasm was prominent as compared to the staining properties of the distal tubules. No nephrocalcinosis was present. Occasional distal tubules were abnormally wide.

Liver. There was an increased lobular pattern with prominent portal tracts, containing numerous bile ducts. These ducts were surrounded by loose connective tissue (Fig. 5) containing collagen but no elastin. The collection of bile ducts were similar to Reye's complexes, although no actual cysts were present. The bile ducts were lined with normal epithelium. The connective tissue contained hemosiderin-laden macrophages. Occasional branches of the hepatic

artery showed defective internal elastic laminae. In addition, the liver lobules showed moderate congestion with dilatation of sinusoids. There was no proliferation of liver cells.

Pancreas. The interstitial tissue was increased and consisted of collagen fibers surrounding collections of sometimes dilated pancreatic ducts (Fig. 6). In general the pancreatic tissue showed increased lobulation owing to broad connective tissue septa having an embryonal appearance and separating the exocrine component into lobules (Fig. 7). The islands appeared normal in distribution.

Among the changes in other organs the following may be mentioned: The skeleton showed irregular mineralization of the growth zone of the ribs and the epiphyses of the tibia and femur with abnormal amount of osteoid and penetration of capillaries into the cartilage from the medullary cavity. The skeletal changes were those of slight rickets. There was normal structure of the

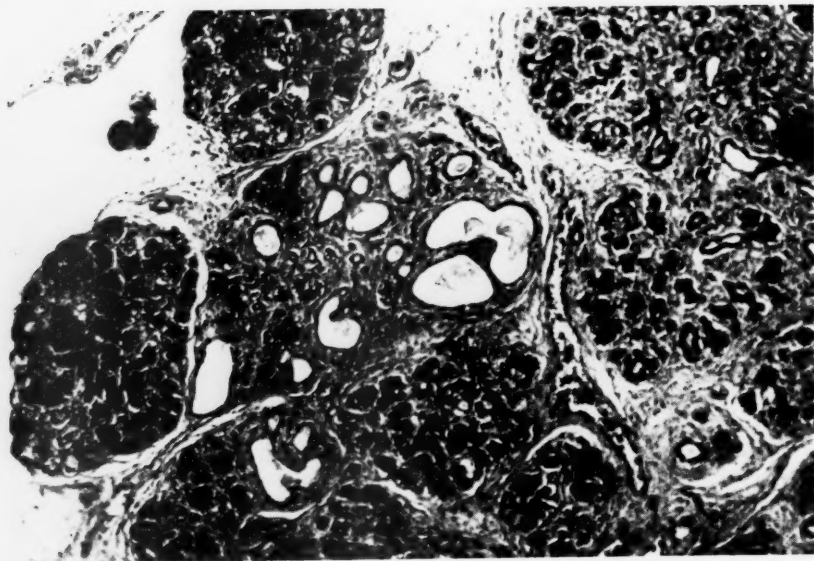


Fig. 6. Case 1. Pancreas. Prominent connective tissue component and dilated ducts. H & E. $\times 48$.

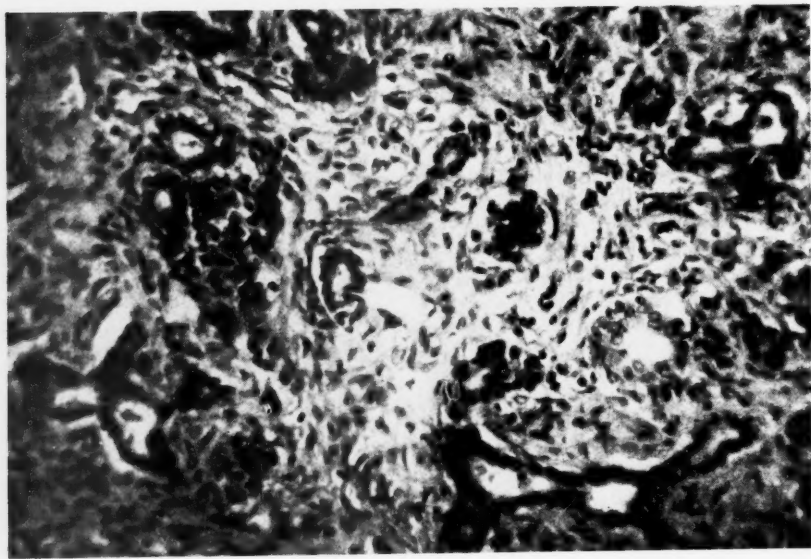


Fig. 7. Case 1. Pancreas. Embryonal connective tissue separating ducts. Small island to the left. H & E. $\times 160$.

parathyroid and thyroid glands, myocardium, lungs, skeletal muscle and spleen.

Final diagnoses: Renal tubular dysplasia with pyelonephritis, dysplasia of liver and pancreas; slight rickets.

CASE 2. Three-week-old male infant, born 4 years after diseased sibling (Case 1). The baby was the product of an uneventful pregnancy and normal labour. Birthweight 4590 g. Wasserman reaction of mother negative. Blood, mother: A, Rh(+). The infant was breast-fed the first week of life, then continued on a half-milk formula. The baby showed apathy, feeding was difficult, and he started to vomit after a few days. Fluid intake per day, 350–400 ml. Jaundice appeared one week after birth, decreased at first, then started to increase. Urine was dark yellow, stools yellow and normal.

The infant was admitted to the Children's Hospital, Linköping, at the age of 13 days. Weight on admission 3400 g, poorly nourished, moderately dehydrated and icteric. There was hepato-splenomegaly, the liver extending 2 fingers below the right costal margin. There was no fever.

Blood: hemoglobin 18.6–19.3 g per 100 ml. RBC 6 mill., WBC 13,900–17,700. Differential count normal. Reticulocytes 0.4 and 1.1 per cent. Thrombocytes 178,000. Blood-group A Rh+. Coombs' test negative.

Urine (summary of several samples): No reducing substances. Albumin occasionally present, about 1 g per l. No urobilinogen, traces of bilirubin and urobilin. Diastase 2 units. A few red and white cells but no casts in the sediment. Excretion of α -amino-acetogeni 26 mg per 100 ml. Paper chromatography of urine did not reveal any pathological amino-aciduria.

The blood sugar level was 85 mg per 100 ml. The serum bilirubin level was 13 and 10 mg per 100 ml. Serum alkaline phosphatase activity, 20 Buch & Buch units. Thymol turbidity, less than 1 unit. Zinc sulphate, 2 units. The non-protein nitrogen was 90, 98, and 88 mg per 100 ml. Serum electrolytes: sodium 153, potassium 5.2, calcium 3.5 mEq

per l. Carbon dioxide combining power less than 9 mEq per l.

The stools were yellow-green and of normal consistency, trypsin positive on gelatin.

Course. Despite parenteral fluid and electrolyte treatment, the infant went rapidly downhill and expired on the 7th day after admission at the age of 20 days.

The clinical diagnosis was renal failure with acidosis and dehydration.

Postmortem examination showed a body of a poorly nourished, underdeveloped male measuring 55 cm in length and weighing 3740 g. The skin and sclerae were moderately icteric. The following pertinent findings were noted. The liver was enlarged, weight 260 g. The external bile ducts were normal and the intestinal content was yellow. The liver was firm, greenish brown and granular and the cut surface showed increased lobulation. The pancreas was firm and the pancreatic duct showed a normal opening on the papilla. The kidneys were small (weight 18 g together) and showed puckered surfaces. The cortex was irregularly reduced in width and the cortico-medullary border was indistinct. The pelvis and the urinary tract were normal.

Histologic examination of the kidneys showed essentially the same changes as those described in Case 1, although they were more severe with numerous medullary and cortical lobules consisting of primitive ducts and tubules. There were several cysts containing proteinous fluid and situated in the cortex. The interstitial tissue contained only very few inflammatory cells, mostly lymphocytes and eosinophils. The changes hardly justified a diagnosis of pyelonephritis. The tubular cells contained bile-stained granules. There were no deposits of mineral salts in the sections. The primitive tubules had the same morphology as those found in Case 1, although they were more often cystic in the present case.

Some of the cysts were of glomerular origin. Many distinctly abnormal primitive glomeruli were found in which the parietal and visceral layer of Bowman's capsule had a cuboidal character, and the capsular spaces

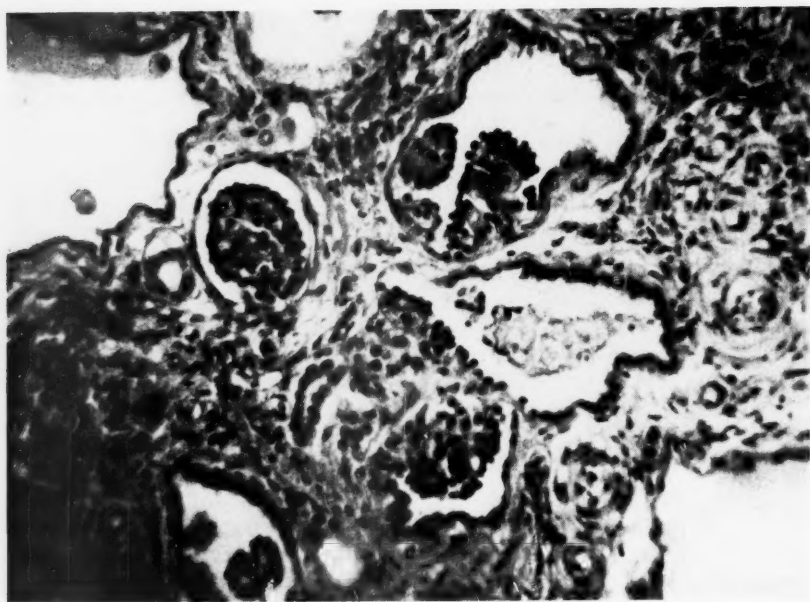


Fig. 8. Case 2. Kidney. Group of cortical cysts, most of them glomerular. H & E. $\times 160$.

of these glomeruli were often irregular (Fig. 8). They were found in the vicinity of primitive tubules and in the areas showing abnormal sinusoidal vascular pattern described below. These abnormal nephrons tended to be grouped together, and the groups were separated by fairly normal-looking nephrons. In the abnormal areas many glomeruli showed focal hyaline sclerosis of the tufts. Although the swan-neck lesion found in Case 1 was looked for intensely, changes only suggestive of this lesion were encountered.

In addition, there were areas with abnormally abundant vasculature and of a sinusoidal character (Fig. 10). The same irregularities of the internal elastic lamellae of the small cortical arteries as present in Case 1, were also found in this case.

Liver. The lobular pattern was increased as in Case 1, although the portal tracts contained more prominent bands of connective tissue in Case 2. In this tissue many bile

ducts were found, with no cystic change, however. The portal tracts showed a slight infiltration of eosinophilic leukocytes. The bile canaliculi and a few bile ducts contained bile thrombi. The sinusoids were dilated. There was no proliferation of liver cells.

The *pancreas* presented less conspicuous change than that of Case 1, inasmuch as the connective tissue was not as prominent, and no cysts were present. The islands of Langerhans were numerous and large, and in the low-power field they almost resembled abscesses.

The osteo-chondral junction showed slight irregularity of the mineralization zone of the vertebrae owing to proliferation of capillaries into the cartilage.

Final diagnoses: *Renal dysplasia, tubular and glomerular, with focal scarring; dysplastic changes in liver with bile stasis; slight dysplasia of pancreas, possibly involving the insulae.*

Discussion

Both siblings exhibited a clinical picture of exactly the same type. Quite soon after birth they developed signs of renal failure. They also developed hepatomegaly and signs of liver disease. The first sibling also showed a moderate anemia, probably secondary to primary renal and hepatic disease. The clinical examination did not disclose any information concerning the pathogenesis of this syndrome.

The histologic changes in the kidneys, liver and pancreas were of a similar type although the degree of involvement of the same organ varied in the two cases. Thus, the renal and hepatic lesions were more marked in Case 2. This was obviously the reason for the more rapid clinical course in that sibling.

The essential renal lesion was the presence of primitive, abnormal, occasionally cystic residues of fetal nephrons, mostly tubular in Case 1 and, in addition, glomerular in Case 2. There were primitive tubules showing cystic changes and a few proximal tubular necks were similar to the swan-neck lesion described in the Fanconi syndrome (Clay, Darmady & Hawkins; Darmady & Stranack). Additional renal changes consisted of abnormal vessels with irregularities of the elastic and sinusoidal pattern of cortical vessels in Case 2. Concomitant chronic pyelonephritis was present in Case 1.

The gross focal maldevelopment of nephrons seen in the two siblings seems to be the major lesion, presumably resulting in focal atrophy, scarring, and, in Case 1, complicated by pyelonephritis. The hypothesis that focal renal dysplasia might attract infection (Marshall; Eric-

son & Ivemark, 1958*a* and *b*) may find support in the cases presented, as the older infant showed pyelonephritis superimposed on the dysplasia, while the younger sibling hardly revealed pyelonephritis. The hyaline glomeruli were similar to those described by Kerenyi & Balogh and classified as congenital glomerulosclerosis.

The significance of the vascular appearance described in this study is at present difficult to evaluate. As pointed out by Marshall abnormal vasculature is no rare lesion in renal dysplasia, and he stresses this feature in a pathogenetic sense.

The renal cysts could be found at any level of the nephron. Microdissection was not carried out, but by that technique Bialestock showed that renal cysts may be glomerular, tubular or ductal, and that in her case the cystic nephrons communicated with the pelvis. She concluded that they were the result of abnormal growth causing giant nephrons to form. The histologic picture of the renal lesions in the present cases is similar to that of Bialestock and seems more compatible with abnormal growth rather than caused by cystic dilatation owing to an hypothetical lack of junction between the metanephrogenic and ureterogenic tubules.

Cystic dysplasia of the liver and pancreas is described in association with familial fetal (Potter) and adult (Rall & Odel) polycystic renal disease. The explanation for this coexistence of usually cystic lesions in various organs is not known. It is generally assumed to be genetically determined but the pathogenesis of the changes is not understood. The findings in the two cases described in

this report do not throw light on the pathogenesis, but the combination of lesions in the kidneys, liver and pancreas is additional evidence of their dysontogenetic origin. A common pathogenetic denominator would be a genetic defect with pleiotropic effect on the target organs at the critical phase of development of the renal tubules, the bile ducts and pancreatic ducts, an arrest of development or abnor-

mal growth in analogy with the syndrome of asplenia or multiple spleens associated with cardiac defects (Ivemark).

The organ distribution and part of the histologic changes in the present cases are similar to that of fetal polycystic disease. Not only is this a support of the present lesions' being dysplastic, but might also mean that there is a common pathogenesis of the two conditions.

Summary

The occurrence of renal, hepatic and pancreatic dysplasia in two siblings is reported. Within the first weeks after birth the siblings developed signs suggesting congenital renal disease with rapid clinical progress resulting in renal failure. Signs of hepatic disease appeared simultaneously. Postmortem examination of the kidneys showed tubular and glomerular local dysplasia with primitive nephrons, small cysts, occasional proximal tubular segments with lesions similar to swan-necks, and vascular abnormalities. The liver and pancreas contained embryonal connective tissue with numerous ducts.

It is concluded that the cases are examples of a syndrome of familial dysplasia of kidney, liver and pancreas, presumably owing to a genetically determined defect. The pathogenesis in relation to polycystic disease is discussed.

Dysplasie familiale des reins, du foie et du pancreas. Un syndrome déterminé probablement d'origine congénitale.

On rapporte l'apparition d'une dysplasie rénale hépatique et pancréatique chez 2 nourrissons.

Au cours des premières semaines après la naissance, les nourrissons montrèrent des signes faisant penser à une maladie rénale congénitale avec une évolution clinique rapide résultant dans une défaillance rénale. Des signes d'une maladie hépatique apparurent simultanément. Un examen post-mortem des reins montra une dysplasie locale tubulaire et du glomérule avec des reins primitifs, de petits kystes, des segments tubulaires proches occasionnels avec des lésions, similaires à des cous de cygne, et des anomalies vasculaires. Le foie et le pancréas contenaient du tissu conjonctif embryonnaire avec de nombreux canaux.

On a conclu que ces cas sont des exemples d'un syndrome familial de dysplasie rénale, hépatique et pancréatique, probablement dû à un défaut génétique déterminé. La pathogénèse en rapport avec la maladie polycystique est discutée.

Familiäre Dysplasie der Nieren, Leber und Pankreas. Wahrscheinlich ein genetisch zu erklärendes Syndrom.

Das Auftreten renaler, hepatischer und Pankreas-Dysplasie bei 2 Säuglingen wurde beschrieben. In den ersten Wochen nach der Geburt zeigten die Säuglinge Zeichen von kongenitaler renaler Erkrankung mit raschem klinischen Fortschreiten, das schliesslich in einer Niereninsuffizienz endete. Zeichen einer Lebererkrankung traten gleichzeitig damit auf.

Post mortem angestellte Untersuchungen der Nieren offenbarten eine lokale, tubuläre und glomeruläre Dysplasie mit primitiven Nephronen, kleinen Zysten, gelegentlich proximal tubulären Segmenten mit Verletzungen ähnlich „Schwanenhälsen“ sowie vaskuläre Verformungen. Leber und Pankreas enthielten embryonales Bindegewebe mit zahllosen Gängen.

Es ergibt sich hieraus, dass diese Fälle als Beispiele für ein Syndrom von familiärer Dysplasie der Nieren, Leber und Pankreas gelten können, vermutlich einem genetisch zu erklärenden Defekt zuzuschreiben. Die Pathogenese in bezug auf Polyzystitis wird diskutiert.

Displasia familiar de riñones, hígado y páncreas. Síndrome de probable índole genética.

Se refiere la aparición de una displasia renal, hepática y pancreática en dos gemelos.

Durante la primera semana después del nacimiento, los gemelos desarrollaron signos que indujeron a pensar en una enfermedad congénita del riñón, de evolución rápida que abocó a la insuficiencia renal. Simultáneamente aparecieron signos de insuficiencia hepática.

El examen necrópsico de los riñones demostró una displasia tubular y glomerular, con nefronas de tipo primitivo, pequeños quistes, algunos segmentos tubulares proximales deformados en S itálica, y anomalías vasculares. El hígado y el páncreas contenían tejido conectivo embrionario con numerosos conductillos.

Se concluye en que estos casos son ejemplos de un síndrome de displasia del riñón, hígado y páncreas, secundaria probablemente a un defecto congénito.

Se discute su patogenia en relación con la enfermedad poliquistica.

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Barnsjukhuset
Göteborg
Sweden

Observations on Goitre in Greece

A Preliminary Report

by SOPHOCLES G. HADJIDAKIS

Goitre has long engaged the attention of Greek medical practice on account of its multiple sporadic occurrence throughout the country. Reports from this country, however, mostly deal with cases, where surgical treatment has been necessary. It is obvious that such restricted consideration of the goitre problem would fail to convey a full and objective picture of this disease entity in terms of incidence, geographical distribution, patients' age and sex, etc. Thus the disease is more frequently encountered than our medical bibliography on the subject would erroneously suggest.

Present Inquiry

As a part of the official State Programme for the Protection of Mother and Child in the country districts in Greece under the auspices of the United Nations (in special cooperation with WHO and UNICEF), which PIKPA launched by request of the Greek Government, a field investigation was carried out during the last 3 years comprising the inhabitants of isolated and inaccessible villages in the northern mountain districts of Greece, as well as with more easily accessible villages in the plains of the same districts in the central and northern parts of the country. This investigation made it possible to estimate the incidence of the disease

in large groups of inhabitants comprising a considerable percentage of the population and to locate the districts in this country where goitre is encountered as an endemic disease.

The greatest percentage of the disease is observed in mountainous districts which can be characterized as "goitrogenous village-foci" and in low-lying or semi-mountainous districts to which these mountainous populations generally move.

Thus, the villages where goitre is observed may be classified into three main groups: (a) "goitrogenous village foci"; (b) "goitre-suffering villages"; (c) "mixed villages", goitre-suffering, with a population of various mountainous origin.

Villages of the first group characterized as "goitrogenous village foci" are very mountainous. Some are habitable throughout the year, while others only for 4-5 months (summer and early fall). The inhabitants of the latter move to the low-lying and southern parts of the country where they live during the winter at a great distance from their original mountainous districts.

"Goitre suffering villages" of the second group are semi-mountainous villages or small towns with mixed high-land and low-land population. High-land families always come from "foci" villages. Some of these families live there only in the winter and spring (8 months), while others have been permanently established for two or three generations. Goitre is not observed in the indigenous population but in families which

come from mountainous villages, and the incidence depends on the percentage of these emigrants from the mountains.

"Mixed villages" of the third group are mostly semi-mountainous. These are mainly newly-built, and their inhabitants are a mixture of various stock-raising people coming from the highlands and not having the homogeneity of the second group. Characteristic of this group is the fact that the incidence of slight goitre among elementary school children is very high, extending to more than 80%.

As to the external conditions (composition of the soil, altitude, position of the village, water-supply, profession and diet of inhabitants), some of the villages in question presented possible predispositional elements of a goitrogenous environment (mountainous, situated on steep slopes, impoverished with questionable water-supply), while others had opposite conditions (being low-lying, relatively rich, with the living conditions of the population not lagging behind those of the neighbouring towns). However, the diet of the inhabitants of all these villages did not lack in proteins, and salt was generally provided by the State Monopoly stores. The chemical analysis made in some villages, showing suspicious goitrogenous external environmental conditions, gave calcium and iodine concentrations in the drinking water and basic foods (wheat-flour, potatoes, beans, maize, salt, mountain herb tea) within the nutritional requirements.

Material

The study is still in progress and is planned to cover more than two hundred villages and small towns. So far 46 villages have been systematically studied. These villages belong to the three above-mentioned groups and may be said to be representative of all the villages giving an average picture of the situation.

Diagnostic criteria

The cardinal sign of the disease is the swelling of the thyroid gland which is diffuse and usually symmetrical and with a soft

consistency. It was sometimes necessary to let the patients lean their heads backwards to detect the swelling.

Results

The incidence of the disease was investigated more extensively during infancy, childhood and adolescence. Examination of 232 infants aged 0-12 months disclosed 68 cases showing swelling of the thyroid gland (36 boys and 32 girls). From a total of 3186 children aged 1-6 years, 1140 showed enlargement of the thyroid, the highest incidence occurring at the age of 5. In another part of the study the pupils of the elementary and high schools in the 46 above-mentioned villages were examined. Of the 11,634 children and youths from seven years of age 6209 were found to be suffering from goitre. Their age and sex distribution is shown in Table 1.

The figures show that there is a higher incidence among the younger children, and with advancing age there is a slow decline for the females and a more rapid for the males, especially after 13 years of age. This makes the sex difference marked among the older children and young adults. Thus, the higher incidence during puberty reported by Davenport, Decourt and Kohn is not confirmed in this material. As for the size of the goitre it seemed that this was more marked among children 11 years old, but no constant trend was found in relation to age.

Furthermore, 1180 15-22 year-old youths of both sexes not included in the above table were examined. Of these 450 were males and 730 females. The results were essentially the same as in the above table.

Only three cases showed signs of hypo-

TABLE 1. *Age and sex distribution.*

Age	Total number examined	M	F	Total number affected	M	F
7	1541	776	765	908	426	482
8	1407	664	743	868	378	490
9	1345	667	678	773	351	422
10	1557	792	745	967	423	544
11	1628	859	769	920	482	438
12	1630	861	769	845	422	423
13	806	471	335	424	220	204
14	492	337	155	168	94	74
15	358	245	113	108	51	57
16	294	191	103	72	25	47
17	263	188	75	65	30	35
18	222	152	70	55	18	37
19	74	22	52	24	2	22
20	37	14	23	12	1	11
Total	11634	6239	5395	6209	2923	3286

thyroidism. The school record of goitrous children in general was in no way below that of nongoitrous ones. The height of goitrous girls during their 11th, 12th and 13th years was below that of the other girls. Above 16 years of age no difference in height was recorded between healthy girls and women and goitrous sufferers.

Among new-born infants the so-called congenital goitre was not found (Laplane, Struve), the newborn being normal and the period of infancy uneventful. These facts were brought out by the systematic observation of children of this category in the Advisory Stations of the mobile units of PIKPA.

Exophthalmic goitre was present in members of 5 families living in villages which cannot be labelled as endemic centers of the disease.

Discussion

Before discussing factors which may give rise to the high incidence of goitre,

a few words would seem in order on the living conditions of the populations of these stock-raising mountain districts. These populations change pasture-grounds continually in search of proper fodder for their flocks and herds, and year by year they move northward in spring and summer, and southward in autumn and winter.

These perennial nomadic movements from North to South and back again require necessarily two homes for each family. Especially during the last 20 years, a part of the nomadic stock-raising mountain population has thus been compelled to intermarry with the more southern farming population of the plains and to settle more or less permanently in the more southern parts. On account of the marriages contracted between the male stock-raisers of the mountains and the female farming plain-dwellers, and the resulting intermixture of the farming population with the mountaineer newcomers, new families arise who live in the

plain but whose genetic origin was originally of mountain stock. In these families endemic goitre is encountered in a much higher proportion than among families of unmixed plain-dwellers. This fact induced us to make a systematic study of the genealogical family trees of all the villages in which goitre was recorded.

Thus we have to date drawn up genealogical trees of control families and goitre-families, both in a considerable number of the "goitrogenous village-foci" and those of the other two groups which receive the population of the first group.

The study of the genealogical trees in question showed in many cases that the affected families in the simply "goitrous" and "mixed" villages were merely younger offshoots of families with roots in goitrous families in villages labelled as "goitre

village-foci". The role of genetics in the production of goitre in the population of the northern departments of Greece seems quite clear. We had many cases in whom the transmission from parents to children was regular although the parents had long been away from the "goitre village-foci", and they presented no clinical symptom. Their children who suffered from goitre had been born in towns and villages far distant from those of their parents.

The whole question of the genetic role in the disease among 403 genealogically investigated families will be the subject of a subsequent and more extensive investigation. Although iodine deficiency could not be proved, the fact that in some cases the goitre diminished following iodine administration indicated that also this factor could play a role.

Summary

A field investigation in the northern districts of Greece disclosed the existence of "goitrogenous village-foci" in an appreciable number of villages, especially in Thessaly, Epirus and Macedonia. Some of these are veritable "goitrogenous village-foci" while others are simply "goitre-suffering villages" presenting an appreciable number of sufferers. In 46 villages, which appeared representative of the rest, a systematic mass-examination was carried out. Goitre was most frequently encountered in children of school age. The frequency according to sex showed that girls up to 13 years of age presented a slightly higher percentage while the incidence of goitre dropped amazingly in boys aged 13 and more. The disease is characterized by its benign nature. Co-existence of goitre and cretinism was observed only exceptionally. The influence of the genetic factor became increasingly evident by studying 403 genealogical trees in various villages.

Observations sur le goitre en Grèce. Communication préliminaire.

Une enquête régionale effectuée dans les provinces du nord de la Grèce a révélé l'existence de « foyers goitrigènes locaux » dans un nombre assez important de villages, notamment en Thessalie, en Épire et en Macédoine. Certains de ceux-ci sont vraiment des « foyers goitrigènes locaux » tandis que d'autres sont simplement des « villages goitreux » où l'on rencontre un nombre assez élevé de personnes atteintes de cette affection. Dans 46 villages, considérés comme représentatifs des localités restantes, un examen de masse systématique fut effectué. On constata que le goitre se rencontrait le plus fréquemment chez les enfants en âge d'école. La statistique de ces cas par sexe a fait apparaître qu'jusqu'à l'âge de treize ans la fréquence du goitre était un peu plus élevée chez les filles et qu'à partir de treize ans, l'incidence de cette affection diminuait dans des proportions étonnantes chez

les garçons. Cette maladie se caractérise par sa nature bénigne. La coexistence du goitre et du crétinisme ne fut observée que dans quelques cas exceptionnels. L'influence du facteur génétique fut mise en évidence par l'étude de 403 arbres généalogiques dans différents villages.

Beobachtungen über Kropf in Griechenland. Vorläufige Mitteilung.

Eine Felduntersuchung in den nördlichen Bezirken von Griechenland enthüllte das Vorhandensein von Kropfbildungsherden in einer beachtlichen Anzahl von Dörfern, besonders in Thessalien, Epirus and Mazedonien. Unter ihnen waren manche Dörfer wahre Kropfbildungsherde, während andere einfach als kropfverseuchte, d.i. eine grosse Zahl von an Kropf leidenden Personen aufweisende, Dörfer anzusehen waren. In 46 Dörfern, welche als repräsentativ angesehen werden konnten, wurden systematische Massenuntersuchungen durchgeführt. Kropf wurde am häufigsten bei Kindern im schulpflichtigen Alter angetroffen. In Hinsicht auf das Geschlecht der befallenen Kinder zeigte es sich, dass bis zu 13 Jahre alte Mädchen einen ein wenig höheren Prozentsatz aufweisen, während bei Knaben im Alter von 13 Jahren und darüber die Kropfinzidenz in erstaunlichem Ausmass abfiel. Die Krankheit ist durch ihre gutartige Natur gekennzeichnet. Gleichzeitiges Bestehen von Kropf und Kretinismus wurde nur ausnahmsweise beobachtet. Beim Studium von 403 Stammbäumen in verschiedenen Dörfern wurde der Einfluss des genetischen Faktors in zunehmendem Mass offenbar.

Observaciones sobre el bocio en Grecia. Aportación preliminar.

Una investigación llevada a cabo en las regiones campesinas de las provincias del norte de Grecia demostró la existencia de "focos bociogenos", en un apreciable número de aldeas, especialmente en Tesalia, Epiro y Macedonia. Algunos de estos son verdaderos "focos bociogenos" radicados en aldeas, mientras que otros son simplemente "aldeas afectas de bocio", con un número considerable de enfermos. En cuarenta y seis aldeas que se tomaron como representativas, se llevó a cabo una exploración en masa sistemática. El bocio era más frecuente en niños de edad escolar. La frecuencia en relación con el sexo demostró un porcentaje ligeramente superior en las niñas mayores de trece años, mientras que la incidencia de bocio caía ostensiblemente en niños de trece o más años. La enfermedad se caracteriza por su naturaleza benigna. La coexistencia de bocio y cretinismo se observó únicamente a título de excepción. Se evidenció la influencia del factor genético al estudiar cuatrocientos tres árboles genealógicos en varias aldeas.

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19, Skoufa Str.
Athens (1)
Greece.

from the Wilhelmina Children's Hospital, Utrecht and from the Central Institute for Nutrition and Food Research T.N.O., Utrecht

Coeliac Disease. VII

Application and Interpretation of the Gliadine Tolerance Curve

by H. A. WEIJERS and J. H. VAN DE KAMER

In a previous publication (11) mention was made of the rise of the glutamine level determined by the method of Prescott & Waelsch (3, 7, 8) in the blood of patients suffering from coeliac disease, after loading with 350 mg gliadine per kg body weight, in contrast to normal children in whom this substance does not increase. The maximum rise of the blood glutamine level was very significantly greater in the coeliac group than in the healthy group.

The gliadine, suspended in buttermilk, was given to the fasting child in the morning; for every gramme of gliadine 25 ml buttermilk was given with 1.25 g saccharose (as a flavouring agent). Special emphasis was placed on the diagnostic value of this tolerance curve. To the results already described, the following are now to be added.

Follow-up of "old" coeliac disease patients (among whom also were some adults who formerly had been in hospital for a longer or shorter time because of coeliac disease, but who held normal positions in society at the time of follow-up) proved that in many of these persons the gliadine

loading test turned out positive (see Tables 1 and 2). This is in contrast with normal persons, in whom no rise above fasting level higher than 40 % was observed after loading with the quantity of gliadine mentioned above.

The gliadine loading test is therefore a sharp criterion, as most of the former coeliac disease patients were not aware of their sensitivity to wheat proteins, and regularly used wheat (bread), as it seemed without ill-effect.¹

The gliadine tolerance curve also affords the means of carrying out a closer investigation into the consequences of wheat consumption in the "milieu intérieur", in this case in the blood. This is highly desirable because, as we believe, coeliac disease is primarily to be regarded as a metabolic disorder.

As after loading with the harmful gliadine the blood glutamine level of coeliac patients rises, one might expect that glutamine, which constitutes 43 % of the gliadine, is identical with the noxious component. However, it has already been shown that this is not true (4). This is the

¹ A number of the patients belonged to a series of coeliac disease patients investigated by Professor G. M. Veeneklaas, M.D., in the Children's Hospital of Leyden.

TABLE 1. *Apparent glutamine content of the bloodplasma of children and adults apparently cured from coeliac disease, after loading them with 350 mg gliadine per kg bodyweight.*

Pa- tients	Age in years	Bodyweight in kg	Loaded with gliadine in g	Apparent glutamine content in mg % of the bloodplasma determined accord- ing to Prescott & Waelsch at hours:						Max. increase in % from the starting level
				0	1	2	3	4	5	
A	14	27	9.4	4.8	6.4	7.1	8.8	7.7	5.5	83
B	8	25	8.6	11.5	12.9	18.3	13.4	12.4	11.5	60
C	11	30	10.6	6.6	8.8	10.2	8.4	7.5	6.6	55
D	23	50	17.5	5.5	6.9	13.9	10.3	8.5	7.2	153
E	23	50	17.5	4.1	7.5	6.4	6.0	5.5	4.2	83
F	15	38	13.3	3.8	7.9	6.6	5.4	5.0	4.2	108
G	12	38	13.4	9.0	12.5	14.5	12.0	9.8	9.3	61
H	40	49	17.0	3.2	6.5	5.6	3.9	3.2	3.2	103
I	36	45	15.8	10.9	11.7	12.5	13.4	11.7	11.3	23
J	8	16	5.5	5.1	8.0	7.8	5.3	4.9	6.3	51
K	17	42	14.7	4.8	5.6	8.6	6.6	4.8	3.7	79
L	10	30	10.5	6.9	8.6	7.7	6.9	6.5	6.9	25
M	29	44	15.4	5.9	7.7	10.4	6.6	5.9	5.9	76
N	14	38	13.1	7.7	8.6	14.0	11.1	10.2	7.9	82
O	23	57	20.0	8.2	—	26.5	14.7	—	—	223
P	10	30	10.3	3.6	—	8.1	5.8	—	—	125
Q	9	23	8.0	7.4	—	12.3	11.1	—	—	66
R	8	28	9.8	5.4	—	6.9	9.3	—	—	72
S	6	22	7.5	4.6	—	9.5	9.0	—	—	107
T	12	30	10.5	11.4	—	14.5	14.0	—	—	27
U	14	36	12.6	6.1	—	6.1	7.0	—	—	14
V	9	39	13.6	8.3	—	8.7	10.1	—	—	22

TABLE 2. *Apparent glutamine content of the bloodplasma of normal children and adults, after loading them with 350 mg gliadine per kg bodyweight.*

Normal individuals	Age in years	Bodyweight in kg	Loaded with gliadine in g	Apparent glutamine content in mg % of the bloodplasma determined according to Prescott & Waelsch at hours:						Increase in % from the starting level
				0	1	2	3	4	5	
A	9	26	9.3	6.3	5.8	5.0	6.3	6.7	5.8	4
B	5	18	6.3	4.5	3.7	4.2	3.7	3.7	4.2	0
C	4	19	6.7	7.4	6.8	9.6	8.5	6.8	—	30
D	7	24	8.5	9.0	—	10.5	10.2	—	—	17
E	4	19	6.7	8.2	—	9.2	10.3	—	—	25
F	26	61	21.5	5.5	—	6.0	7.7	—	—	40
G	37	52	18.1	12.2	—	13.1	13.1	—	—	7
H	54	64	22.2	6.4	—	6.8	6.4	—	—	6
I	82	83	28.9	5.0	—	5.8	7.0	—	—	40
J	33	86	30.1	8.6	—	11.1	8.6	—	—	29
K	48	79	27.7	8.5	—	10.8	8.8	—	—	27
L	56	71	24.9	6.3	—	7.0	7.9	—	—	25
M	31	70	24.3	7.2	—	8.1	8.1	—	—	12
N	55	63	22	8.8	8.8	10.9	9.1	—	—	24
O	15	51	17.8	11.9	—	12.9	11.9	—	—	8
P	30	68	23.8	10.1	—	11.1	9.7	—	—	10
Q	32	69	24.2	6.6	—	6.7	6.3	—	—	2
R	55	57	20	6.3	—	8.1	7.4	—	—	29

reason why the possibility has been advanced that the harmful action of gliadine might be caused by glutamine in peptide form, and the question is therefore raised whether the method of Prescott & Waelsch, which we always used to assess (or estimate) the "glutamine" level of the blood after loading with gliadine, determines glutamine in peptide form as well as free glutamine. Our findings show that this form of glutamine is also accounted for by "apparent glutamine" of Prescott & Waelsch.

It was therefore necessary to investigate whether the rise of the gliadine tolerance curve in coeliac disease patients is caused by free glutamine or by glutamine in peptide form.

This can be done by using the method of Archibald (1, 2) determining only free glutamine by the action of glutaminase. Subsequently the content of peptide-glutamine can be calculated as the difference between the "glutamine" determined according to Prescott & Waelsch and Archibald.

Methods

A. Method of Prescott & Waelsch

This method (7), slightly altered by the same authors in 1947 (8), is used with the following minor modifications.

Three tenths ml heparin plasma and 0.3 ml trichloroacetic acid solution 7.5% are thoroughly mixed. Three tenths ml of the filtrate is placed on the Al_2O_3 (Brockmann) column (with 1 mg PbCO_3 on top) after neutralization on bromophenol blue (instead of bromothymol blue). After washing the column with H_2O until 4 ml eluate is collected, 2 ml 6 N HCl is added to the eluate, following which the mixture is hydrolyzed, neutralized and made up to 10 ml.

Six ml is run over the second Al_2O_3 column, followed by washing with 2 ml H_2O . Subsequently the glutamic acid is eluted from the column with 4 ml 0.5 N acetic acid and determined as described in the original paper.

Slight suction is applied to make the fluids pass through the Al_2O_3 columns.

The capryl alcohol is purified by boiling 1 litre for 2 hours with 5 g NaOH + 5 g aluminium powder + 5 ml H_2O followed by distillation. The determination has been checked several times by adding a known amount of glutamine to a trichloroacetic acid filtrate of plasma, from which 90–100% was recovered.

Recently, using a new batch of Al_2O_3 , the method as described above did not give good results. It appeared to be necessary to lower the quantity of NaCl passing the Al_2O_3 column. Therefore the neutralized trichloroacetic filtrate after passing for the first time an Al_2O_3 column (covered with 1 mg PbCO_3), is evaporated to dryness in a boiling waterbath under a stream of nitrogen. The residue is dissolved in 0.4 ml 2.0 N HCl and hydrolyzed in the usual manner during 1 hour in a boiling waterbath under reflux. After cooling and neutralizing on bromophenol blue the volume is made up to 7 ml and 4 ml is brought on the Al_2O_3 column. Next the column is washed with 2 ml H_2O and eluted with 2×2 ml acetic acid 0.5 N. The reaction with ninhydrin is performed now as described in the original paper.

B. Method of Archibald

This method (1, 2) depends on the determination of NH_3 liberated by the action of glutaminase. As a source of glutaminase a suspension of *Clostridium perfringens* S.R. 12 (*Clostridium welchii*) is used, prepared according to Krebs (5).

The microquantities of NH_3 (0.1 to 3.0 μg) released by the glutaminase, are determined according to Lubochinsky & Zalta (6). Since this method is very accurate, giving a very stable colour, it is preferable to the well-known method of Nessler.

Preparation of the medium for Clostridium perfringens S.R. 12.

Yeast extract 5 g, Tryptone (Difco) 15 g, NaCl 2.5 g, L-cysteine HCl 0.5 g, Glucose 20 g, Distilled water 750 ml.

Dissolve by boiling and adjust if necessary to pH 7.2–7.5. Sterilize for 20 minutes at 121°C, and cool down. Then take, under aseptic conditions, a sample of 50 ml and adjust to pH 7.2–7.3 with NaOH 10%. Notice the quantity of alkali needed, and add a proportional quantity of sterile NaOH 10% to the medium and check the pH (7.2 to 7.3) again working under sterile conditions. Drive out the oxygen by boiling the medium for a short time. Cool quickly, do not shake any more.

Maintenance of Clostridium perfringens S.R. 12.

Transfer—by means of a pipette—1 ml of a culture of the bacteria, 3 to 4 weeks old, into a culture tube containing 10 ml of freshly prepared medium. Close off the inoculated medium with a layer of 2 cm sterile paraffin oil and incubate for 24 hours at 37°C.

Keep the culture, after growth (turbidity) has been observed, for 3–4 weeks in a refrigerator at 5°C. After this period the culture has to be subcultured again in freshly prepared medium.

Always maintain in this way four tubes with *Clostridium perfringens* S.R. 12.

Preparation of about 10 g washed Clostridium perfringens S.R. 12.

Divide 4 l freshly prepared medium into two equal portions into two flasks of 5 l. Bring to boiling temperature, cool down quickly and inoculate each 2 l medium with 2×10 ml *Clostridium* culture, incubated for 24 hours at 37°C. Close off with a 2 cm layer of sterile paraffin oil.

Incubate the flasks for 24 hours at 37°C (abundant quantities of gas will develop). Keep the flasks for 4 to 5 days at 5°C to allow the bacteria to settle.

Decant the largest part of the supernatant fluid and suspend the bacteria in the remaining liquid. Then collect the bacteria by centrifuging and wash five times with 25 ml of a sterile NaCl solution of 0.85%. Weigh the bacteria ("wet weight") and suspend every 2 g in 10 ml 0.2 M acetate-buffer pH 4.5.

Keep the suspension of the bacteria in a refrigerator at 5°C.

Determination of glutamine by incubation with Clostridium.

Two ml plasma is mixed thoroughly with 2 ml trichloroacetic acid 7.5% and centrifuged. Two ml of the centrifugate is neutralized on bromophenol blue and filtered over an Al_2O_3 column according to Prescott & Waelsch and rinsed with H_2O up to a volume of 6 ml. After addition of 0.5 ml acetate-buffer 0.2 M of pH 4.9, 1 ml of the filtrate, in duplicate, is incubated for 1 hour at 37°C with 0.2 ml *Clostridium* suspension diluted 1:1. The incubation is carried out in penicillin flask of 25 ml. Before incubation the mixture is warmed to 37°C.

Next the determination of the NH_3 set free by the glutaminase of the *Clostridium* suspension is carried out, using the same penicillin flask, according to the principles given by Seegmiller *et al.* and Seligson & Seligson (9, 10). The NH_3 is liberated by adding 1 ml of a saturated K_2CO_3 solution in H_2O . The flask is immediately closed with a rubber stopper with a small glass tube with a bulb at its end fixed in it. The bulb is moistened with a very thin film of H_3PO_4 1 M. The flask is attached to a wheel so that the glass tube is in a horizontal position and the wheel is turned for 1 hour at 37°C (about 45 r.p.m.). Afterwards the bulb is rinsed quantitatively with 2 ml distilled water and the NH_3 is determined according to Lubochinsky-Zalta (6), somewhat modified: viz. use 0.6 ml sodium phenolate, 0.6 ml phosphate, 0.6 ml sodium-nitroprusside solution, 0.2 ml sodium-hypochlorite and make up to 6 ml. The colour is read off in small test tubes of 2 ml in a photo-electric colorimeter at 610 μ (procedure I).

The NH_3 figures are read off from a standard curve made with the aid of a solution of $0.3 \mu\text{g}$ analytically pure $(\text{NH}_4)_2\text{SO}_4$.

A blank determination is carried out as follows.

To a same quantity of NaOH used to neutralise the trichloroacetic acid filtrate of the plasma mentioned above, trichloroacetic acid 7.5% is added till neutral reaction on bromophenol blue. After filtration and washing over an Al_2O_3 column the eluate is filled up with water to 6 ml. From this solution 1 ml in duplicate is used to determine the blank of the *Clostridium* suspension. Therefore 0.5 ml acetate-buffer, 0.2 ml *Clostridium* suspension 1:1 are added and after incubation for 1 hour at 37°C the NH_3 is determined according to the procedure mentioned above (Procedure II). Another 1 ml in duplicate is used to determine the blank of the reagents by adding only 0.5 ml acetate-buffer, followed by the determination of the NH_3 (Procedure IV).

Calculation

The glutamine content of the plasma is calculated by reading first in the colorimeter the colour developed by the NH_3 by Procedure I against the colour developed by Procedure II.

The result has to be corrected, however, for the preformed NH_3 present in the plasma. Therefore a trichloroacetic acid filtrate of the plasma filtered over an Al_2O_3 column has to be run through the whole procedure without *Clostridium* (Procedure III). The NH_3 colour developed in this way has to be measured against the NH_3 developed by the reagents (Procedure IV).

Thus the glutamine is calculated as:

$$[(\text{I} - \text{II}) - (\text{III} - \text{IV})] \times 8.59.$$

The factor 8.59 is used to convert the ammonia to glutamine; it is calculated as the quotient from the molecular weight of glutamine (146) and the molecular weight of NH_3 (17).

The lower ends of the small glass tubes, when not in use, are to be kept in a 85% H_3PO_4 solution. Just before use they must

be rinsed with distilled water. Then the tubes must be dried with a filter paper, *with exception of the bulbs*. Subsequently the bulb is moistened with H_3PO_4 solution 1 M. There is an advantage in fixing a second bulb about 0.5 cm above that at the end of the tube, to prevent the H_3PO_4 film from flowing down during the rotation on the wheel.

Results

The results according to the Archibald method give a practically flat line in coeliac patients in whom the Prescott-Waelsch curve shows a rise after loading with 350 mg gliadine per kg body weight (see Fig. 1 and Table 3).

The fasting values determined by these two methods, are similar. No difference is to be expected because under normal conditions fasting blood does not contain peptides, apart from glutathione.

This substance, however, cannot interfere, since it is not accounted for by the determination according to the Prescott-Waelsch method, because it is fixed by the thin layer of PbCO_3 on the Al_2O_3 . Neither can pyrrolidone carbonic acid influence the results of this method of determination, because this substance is absorbed on the Al_2O_3 column, so that it is likewise withheld from the mixture of amino-acids.

From these results we should like to conclude that in coeliac patients the "glutamine" rise is caused by peptides containing glutamine and not by free glutamine.

Even though it seems probable to us that there exists a very close relationship between these peptides and the harmful effect of the wheat, it should not be forgotten that the mechanism of this action is so far not understood.

TABLE 3. *Apparent glutamine content according to Prescott-Waelsch and true glutamine content according to Archibald in the bloodplasma of coeliac patients after loading them with 350 mg gliadin per kg bodyweight.*

Name	Age in years	Body-weight in kg	Loaded with gliadin in g	Apparent glutamine content in mg % of the bloodplasma after hours:			Increase in % of the starting value	True glutamine content in mg % of the bloodplasma after hours:			Increase in % of the starting value
				0	2	3		0	2	3	
s	6	22	7.5	4.6	9.5	9.0	107	4.9	6.5	6.4	33
t	8	28	9.8	5.4	6.9	9.3	72	6.6	6.3	7.0	6
u	9	23	8.0	7.4	12.3	11.1	66	5.8	4.9	6.1	5
v	10	30	10.3	3.6	8.1	5.8	125	3.0	4.5	3.9	50
w I	6	20.7	7.3	7.7	11.5	9.6	49	7.4	8.0	9.2	24
w II (one month later)	6	20.7	7.3	5.2	11.1	12.3	139	6.1	7.7	6.4	26

Discussion

In our opinion, a difference in "glutamine" level determined by the Prescott-Waelsch or Archibald method, respectively, must be based on the presence in the blood of peptides containing glutamine, although absolute proof of this has not been rendered.

When the question is raised what may be the cause of the presence of peptides in the blood, one might think of a state of still incomplete development of the proteolytic enzyme systems in the lumen or in the intestinal cells, so that food proteins are not completely broken down to amino-acids, but subsequently are taken up in the form of peptides. This might be comparable with the observations in premature and newborn children, in whom undesired reactions sometimes arise due to the absorption of peptides when proteins are consumed, while the function of their intestinal cells is not yet fully developed.

Another possibility is that the proteolysis is only inhibited e.g. by accumulation

of breakdown products, due to the hypotony of the intestine and the defective circulation associated with this. Gliadine, especially, with its high glutamine content, might be able to exert an extra harmful influence in this respect, when the ammonia formed from the glutamine is not sufficiently eliminated. Absorption of peptides might therefore also be caused by this inhibited proteolysis.

A strong support of the latter conception is the appearance or non-appearance of glutamic acid-peptides in the blood when—as explained above—the patient is loaded with desamidated gliadin from which the ammonia has or has not been removed by dialysis.

An argument in favour of these considerations is also the temporary wheat sensitivity of babies recovering from a serious nutritional disturbance in the phase in which their intestine is still hypotonic.

When we consider the consequences of

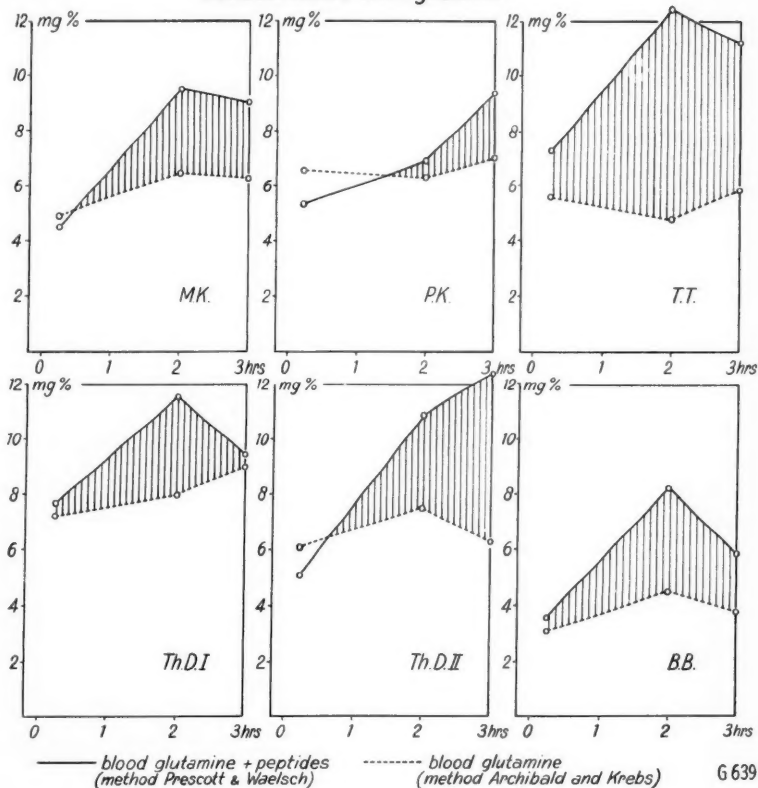
Celiacs loaded with gliadine

Fig. 1.

the presence of glutamine-containing peptides in the blood, it is *a priori* not excluded that they might provoke an allergic reaction as assumed e.g. by Berger (3 a). As a matter of fact, some children sensitized with wheat promptly show a catastrophic reaction to very small quantities of wheat. In the majority of coeliac disease patients sensitized with wheat, however, the manifestations of wheat sensitivity do not develop earlier than two weeks or even

later after every inclusion of wheat in the diet. Neither do they develop shock, collapse, etc. In our opinion a "normal" reaction of a coeliac disease patient to wheat is therefore based on a genuine metabolic disorder caused by the presence of glutamine-containing peptides, while in the case of the child who also has an allergic constitution, it is the catastrophic allergic reaction which is first and foremost provoked.

Summary

The rise of the glutamine level of the blood of coeliac disease patients after oral loading with gliadine, as demonstrated before, was subjected to a closer analysis. It was found that this rise was not caused by free glutamine, but probably by peptide-bound glutamine. Some explanations for the presence of these peptides in the blood are discussed.

Maladie coeliaque VII: Application et interprétation de la courbe de tolérance du gliadine.

Comme on l'a déjà démontré, l'élimination du taux de glutamine dans le sang des malades souffrant d'une affection coeliaque après administration per os de gliadine, a été analysée de plus près. On a trouvé que cette élévation n'est pas provoquée par la glutamine libre, mais probablement par la glutamine liée à des peptides. Quelques explications sur la présence de ces peptides dans le sang sont données.

Coeliakie VII: Bedeutung und Darstellung der Gliadin Toleranzkurve.

Das Anschwellen des Glutaminspiegels des Blutes bei Coeliakie-Patienten wurde nach oraler Verabreichung mit Gliadine, wie vorher beschrieben, einer näheren Analyse unterzogen. Es wurde gefunden, dass das Ansteigen nicht durch freie Glutamine, wahrscheinlich durch an Peptide gebundenes Glutamin verursacht wurde. Einige Erklärungen für die Gegenwart dieser Peptide im Blut werden besprochen.

Enfermedad celiaca VII: Aplicación y interpretación de la curva de tolerancia a la gliadina.

Se someten a un estrecho análisis el aumento del nivel de glutamina en sangre de los enfermos afectos de enfermedad celiaca después de la administración oral de gliadina, demostrado anteriormente. Se observó que este aumento no era provocado por la glutamina libre, sino probablemente por glutamina ligada a péptidos. Se discuten algunas explicaciones de la presencia de estos péptidos en la sangre.

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Central Institute for Nutrition and Food
Research T.N.O.
Utrecht
The Netherlands

From the Department of Virus Research, Karolinska Institutet, School of Medicine, and the Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden

Comparative Studies on Measles and Distemper Viruses

by GUN CARLSTRÖM

Introduction

The question whether canine distemper virus (C.D.V.) may produce disease in man has long been considered. In the medical literature it has from time to time and by different authors been discussed whether the viral agent that causes distemper in dogs gives rise to infections in man (Bryan, 1928; Nicolle, 1931; Whitney, 1943). Most of the theories on this subject were based on clinical or experimental observations, but the question remained unanswered. In 1953 Adams reported that he had been able to demonstrate a C.D.V.-neutralizing substance in human gamma globulin and human serum. This observation, which suggested that infection with C.D.V. or some immunologically related agent may affect man, prompted the investigations reported here.

A re-examination of Adams' observation was made. By employment of neutralization tests in chick embryo serum samples were examined from adults who had earlier been in contact with dogs infected with canine distemper. In all the persons investigated C.D.V.-neutralizing activity was demonstrated. The same was the case in 2 children more than 10 years of age

and selected at random, while negative result was obtained with serum from children less than 3 years of age (Carlström, 1956). The results of these preliminary investigations favoured the view that serological immunity against canine distemper can be acquired by humans, and further study of the problem seemed to be justified.

Initially attempts were made to demonstrate the occurrence of C.D.V. infections in children. These attempts were not successful. Instead, during the course of the work an evident relationship between C.D.V.-neutralizing activity and infections with measles was found. As a consequence of these results the work was gradually concentrated on studies of measles virus (M.V.) with special reference to a possible immunological relationship between M.V. and C.D.V.

Canine distemper in dogs and measles in children show some clinical similarities. Except in dogs, canine distemper occurs mainly in foxes, wolves and ferrets. Measles may, besides human subjects, also affect monkeys. Canine distemper is characterized by fever, conjunctivitis, rhinitis, bronchitis, pneumonia, and gastroenteri-

tis. In the later stage of the illness the central nervous system may be involved. Skin lesions in the form of superficial pustulous exanthema have been described. Fever and catarrhal symptoms are also characteristic of measles, and involvement of the central nervous system may also occur. On the other hand, in canine distemper there are no manifestations corresponding to the skin lesions which are a prominent feature in measles. Exanthema has been described in connection with canine distemper, but this symptom is relatively rare, it does not dominate the clinical picture and the nature of these lesions seems to differ from the typical measles eruptions.

The epidemiological analogies between the two conditions are striking. Both are highly contagious diseases, which require rigid measures of isolation to prevent spread of the infection to susceptible subjects. Both diseases affect mainly the young population and adults are usually immune. Measles and distemper also show similar seasonal fluctuations.

It is now known that the two diseases are caused by viral agents. In comparing known virological data concerning M.V. and C.D.V., some parallelism can be recognized. Thus, we are probably concerned with two medium-sized viruses (Bindrich, 1954; Benyesh *et al.*, 1958), and both are highly labile. Both C.D.V. and M.V. have been cultivated in chick embryo (Rake & Shaffer, 1939; Haig, 1949; Cabasso & Cox, 1949) as well as in baby mice (Morse *et al.*, 1953; Imagawa & Adams, 1958) and baby hamsters (Gutierrez & Gorham, 1955; Cabasso *et al.*, 1955; Burnstein *et al.*, 1958). Both propagate *in vitro* in cultures of trypsinized kidney cells (Enders & Peebles,

1954; Rockborn, 1958), and give rise to similar cytopathogenic changes. Finally, it should be mentioned that in infection with these two viruses similar histopathological changes with giant-cells and inclusion bodies have been demonstrated (Pinker-ton *et al.*, 1945).

The object of the following study is an examination of the immunological relationship between M.V. and C.D.V.

C.D.V.-Neutralizing Activity in Human Serum

When the preliminary investigations by the present writer were started in 1953, in-ovo neutralization test was, for practical reasons, the only reliable serological canine distemper test. In the same year, however, Morse *et al.* reported that they had successfully adapted C.D.V. to baby mice by employment of intracerebral inoculation. This should provide a possibility to carry out the neutralization test by inoculation in mice instead of in eggs. Thus attempts were made to cultivate egg-adapted C.D.V. in mice and to elaborate a neutralization test technique by means of intracerebral inoculations in mice. These attempts were successful (Carlström, 1956). The mouse-adapted strain of C.D.V. is now in its 130th mouse passage and the titer expressed as the logarithm of LD₅₀ is at about 2.5. It has been possible to transfer virus from the 117th mouse-passage back to chick embryo, where lesions, typical for C.D.V., were produced on the chorioallantoic membrane. The addition to this virus of immune serum from a dog that had been inoculated with ferret-adapted C.D.V. prevented the development of such lesions in the egg.

While this reproducible mouse test for the demonstration of C.D.V.-neutralizing activity was elaborated, Gutierrez & Gorman made corresponding studies published in 1955. The results of the two investigations were unanimous.

By employment of the mouse test technique, serum samples from adults and from children of different ages were examined for C.D.V.-neutralizing capacity (Carlström, 1956, 1957). It was found that all the examined sera from adults and children more than 11 years old were positive. With declining age the incidence of positive sera decreased, and in children between the ages of 1 year and 3 years C.D.V.-neutralizing capacity was demonstrated in a few cases only. For children less than 3 months old the result was the same as for adults. The age-distribution was found to resemble the typical immune response curve to common human viral infections. The case-material, methods, and detailed results have been published elsewhere (Carlström, 1956, 1957).

The Relation between C.D.V.-Neutralizing Activity in Human Serum and Infections with Measles

From the above observations it was inferred that the agent giving rise to C.D.V.-neutralizing activity in human serum should occur frequently in man. A priori, it was reasonable to assume that this agent could be related to or identical with some known, infectious agent. Therefore, in search for past viral infections, retrospective analyses of the histories of previously investigated children were made. Correlation of the serological and historical data exhibited an evident relationship between the presence of C.D.V.-

neutralizing substances in serum and a past history of measles (Carlström, 1957, 1958). This observation led to a serological study of measles patients, by which a significant rise in C.D.V.-neutralizing titer from the acute to the convalescent phase was found. For detailed data the reader is referred to Carlström, 1957, 1958.

From these results it was apparent that the presence of C.D.V.-neutralizing activity in human serum was not necessarily related to contact between C.D.V.-infected animals and man. This was further illustrated by examination of serum samples from Icelandic children (Carlström, 1958). Distemper has not occurred in dogs in Iceland for many years, but, nevertheless, C.D.V.-neutralizing activity was demonstrated in sera from these children.

The investigations reported in the foregoing suggested an immunological relationship between C.D.V. and M.V. and it could be presumed that infection with measles is associated with the presence of C.D.V.-neutralizing substances in human serum. In the following an account will be given for experiments making it possible to distinguish between distemper virus and measles virus, and between distemper serum and measles serum (Carlström, 1958). It should be pointed out that in all the children investigated positive sera showed properties characteristic of measles serum. However, the possibility of C.D.V. infection occurring in man may not as yet be ruled out with certainty.

Cross-Serological Tests with Measles and Distemper Viruses

The immunological relationship between M.V. and C.D.V. required further investigation. The serological tests available for this

purpose were complement-fixation test (Enders & Peebles, 1954; Mansi, 1955), and neutralization test (Cabasso & Cox, 1949; Enders & Peebles, 1954). Since the complement-fixation test is often less specific and requires much work for the production of standardized antigens, the neutralization test was considered preferable. By the existing methods the M.V.-neutralization test could be carried out in tissue culture only, and the C.D.V. test, for practical reasons, in eggs only. It was desirable to ensure, as far as possible, identical experimental conditions for the two viruses and preferable to use a common animal host. A mouse test for the measurement of C.D.V.-neutralizing activity has been described in the foregoing, and by application of the technique used for C.D.V., attempts were made to cultivate measles virus in suckling mice. In a previous paper (Carlström, 1958) an account was given of adaptation to mice of a human-kidney-adapted measles virus by intracerebral inoculations, and of the elaboration of a mouse test for the demonstration of M.V.-neutralizing substances. Measles virus has now been carried through 30 passages in baby-mouse brain, and the titer expressed as the logarithm of LD_{50} is at about 2. Detailed data concerning these investigations will be found in the above-mentioned article (Carlström, 1958).

Recently, attempts to transfer mouse propagated M.V. back to human kidney tissue have yielded positive results with virus carried through 19 mouse passages. The equivocal results of numerous previous attempts may be due to the trypsinization technique, which was changed prior to the successful trial. Instead of leaving the tissue in trypsin solution for 12 hours at 4°C, 20 minutes at room temperature was tried. 0.2 ml of a 40 per cent suspension of lyophilized mouse brains was employed as inoculum. Cytopathogenic changes, typical for M.V., were produced and serial transfer of virus was accomplished with infected fluids serving as inoculum. Serum of a rabbit immunized with human kidney propagated M.V. prevented the development of such cytopatho-

genic changes while pre-immunization rabbit serum had no neutralizing capacity.

It has thus become possible to carry out neutralization tests in baby mice for demonstration of both M.V. and C.D.V.-neutralizing activity. The techniques were employed in cross-neutralization titrations (Carlström, 1958), the two viruses being tested against fivefold dilutions of measles and distemper sera. The highest fivefold serum dilution protecting more than 50 per cent of the test mice was taken as the neutralizing titer. By cross-neutralization titrations an antigenic difference between M.V. and C.D.V. was demonstrated. The heterologous titer of measles serum was consistently lower than the homologous titer, while the corresponding titers of distemper serum were found almost equal. The extent of the antigenic relationship between the two viruses (R) was estimated from the titration results by application of the formula $R = \sqrt{r_1 \times r_2}$ (Archetti & Horsfall, 1950; Chu *et al.*, 1950), where r_1 is the ratio of heterologous to homologous titer of serum 1 and r_2 the same ratio of serum 2. The value of R equal to 1 indicates that the agents tested are antigenically indistinguishable. For M.V. and C.D.V., tests with different pairs of sera gave R equalling 1/5, which indicates a significant antigenic difference between the two viruses.

The ratio of heterologous to homologous titer of measles serum (r_m) was found to be 1/25 and that of distemper serum (r_d) 1. This provided a means to distinguish between measles serum and distemper serum by tests against known viruses and, *vice versa*, between measles virus and distemper virus by tests against known sera.

Convalescent sera from measles patients and children's sera containing C.D.V.-neutralizing substances were titrated against the two viruses (Carlström, 1958), and in all cases the ratio of C.D.V.-neutralizing titer to M.V.-neutralizing titer was less than 1 (1/5 to 1/125, usually 1/25). It could thus be presumed that the neutralizing activity in the investigated patients had been caused by infections with measles virus.

Experimental Infections with Measles and Distemper Viruses

It is evident that M.V. and C.D.V. possess many common properties. As regards host tropism, however, there is reason to assume specific differences. At present, investigations concerning the pathogenicity and antigenicity of the two agents to different animal species are in progress. The above reported investigations show that M.V. and C.D.V. are immunologically related and give rise to cross-neutralizing substances. If C.D.V. is non-pathogenic to man but gives rise to M.V.-neutralizing substances in humans, it should be suitable for use as a vaccine against measles. The reverse—the possibility to use measles virus for vaccination against distemper—should also be considered. The experiments now in progress will be published elsewhere. The results of the investigations carried out up to date will only be briefly mentioned.

Dogs inoculated with dog-kidney-adapted measles virus did not develop any clinical symptoms. After repeated inoculations both M.V.-neutralizing and C.D.V.-neutralizing substances were found in serum. In dogs that were inoculated once only no neutralizing activity was demonstrable, and, therefore, it is not probable that any propagation of measles virus occurred in the dogs.

Ferrets were inoculated with human-kidney-adapted measles virus. In all the animals M.V.-neutralizing substances of low titer were demonstrated in serum before inoculation. All ferrets became ill with cerebral symptoms or respiratory disorders, though not typical of distemper. Three of four animals died. In the surviv-

ing ferret an increase in M.V.-neutralizing activity was found after recovery.

Monkeys inoculated with egg-adapted C.D.V. did not develop any clinical symptoms. Two to three weeks after inoculation C.D.V.-neutralizing and M.V.-neutralizing substances of relatively high titers were demonstrated. The activity remained for at least two months. There is, however, reason to suspect an outbreak of inapparent infection with measles among the monkeys while the experiments were in progress, and any definite conclusions must await further investigations.

Two *infants* with severe congenital malformations were inoculated with egg-adapted C.D.V. The inoculation did not provoke any clinical manifestations. In one infant C.D.V.-neutralizing substances in undiluted serum and M.V.-neutralizing substances in a serum dilution of 1/25 were demonstrated before inoculation. In the other child no neutralizing activity was demonstrated. In the first infant C.D.V.-neutralizing activity increased after inoculation and appeared in a serum dilution of 1/25, while the M.V.-neutralizing titer remained unchanged. In the other case neutralizing substances against both C.D.V. and M.V. were demonstrated in undiluted serum after inoculation.

The full account of these investigations and further experiments along these lines will be given elsewhere. The relation between neutralizing activity in serum and protection against infection is also under examination.

The Classification of Measles and Distemper Viruses

Enders, in 1954, suggested a classification of viruses based on the cytopatho-

genic effect of different agents on cells cultivated *in vitro*. His Group IIIb includes viruses that produce large polynuclear syncytia and vacuolisation of the tissue. This group comprises M.V. and an agent isolated from monkey kidney. Ruckle, in 1958, has shown that there are at least two different "monkey agents". One, the "foamy agent", differs antigenically from M.V., while the other, the so-called M.I.N.I.A. (monkey intranuclear inclusion agent) is immunologically indistinguishable from M.V. The question whether M.I.N.I.A. would be identical with M.V. has not yet been settled.

The virus subcommittee of the international nomenclature committee (Andrewes, 1955) has proposed 8 criteria to be used in classifying viruses: (1) morphology and methods of reproduction; (2) chemical composition and physical properties; (3) immunological properties; (4) susceptibility to chemical and physical agents; (5) natural methods of transmission; (6) host, tissue, and cell tropisms; (7) pathology, including formation of inclusion bodies; (8) sympto-

matology. The first five points refer to more fundamental and stable properties, while the last three are fairly unstable and, hence, as a basis for classification they are less reliable.

As regards both M.V. and C.D.V. our knowledge is as yet incomplete on many points, but the investigations reported here show a definite immunological relationship between the two viruses. One of the most important criteria set forth by the international nomenclature committee for referring two agents to the same virus group, has thus been fulfilled. Further evidence is provided by the common characteristics of M.V. and C.D.V. concerning tissue and cell tropism, pathology and symptomatology, as was mentioned in the foregoing. Polding & Simpson in 1957, and Goret *et al.* in 1957, have presented evidence of an immunological relationship between rinderpest virus and C.D.V. Tentatively it seems justifiable to propose a virus group comprising 3 agents: measles virus, distemper virus and rinderpest virus.

Summary

Canine-distemper virus (C.D.V.) was adapted to suckling mice, and a test for the measurement of C.D.V.-neutralizing activity was elaborated. The distribution of C.D.V.-neutralizing substances in various age groups in man was found to resemble the typical pattern of immune response to human viral infections. An evident relationship between the presence of C.D.V.-neutralizing activity in human sera and past infection with measles was found. Also, in measles patients there was a significant rise in C.D.V.-neutralizing titer from the acute to the convalescent phase.

Measles virus (M.V.) was adapted to baby mice, and a test for the demonstration of M.V.-neutralizing activity was elaborated. M.V. and C.D.V. and corresponding antisera were used for cross-serological titrations in baby mice. The two agents were found to be immunologically related but an antigenic difference was demonstrable.

A group of viruses is proposed, comprising measles virus, distemper virus, and rinderpest virus.

A preliminary report is given of experiments concerning the antigenicity and patho-

generality of M.V. and C.D.V. to various animal species, the intention being to investigate the possibility of vaccinating with C.D.V. against measles and *vice versa*. Preliminary results on these experiments are given.

Etudes comparatives des virus de la rougeole et de la maladie de Carré.

L'auteur a adapté à des souris nouveau-nées le virus de la maladie de Carré (V.M.C.), et mis au point une réaction permettant d'estimer l'activité neutralisant ce virus. La distribution, chez l'homme, en fonction de différents groupes d'âge, des substances neutralisantes correspond au type de réponse immunitaire des infections virales humaines. Il existe une relation nette entre la présence dans les sérums humains d'une activité neutralisant le V.M.C. et une infection rougeoleuse antérieure. En outre, dans les sérums de malades atteints de rougeole, on peut constater, entre le début de la maladie et la phase de convalescence, une augmentation significative du titre de l'activité neutralisante. Le virus de la rougeole (V. R.) a été, lui aussi, adapté à des souris nouveau-nées, et une réaction pour la mise en évidence d'une activité neutralisant le V.R., mise au point. Les V.R. et V.M.C., et les immunosérums correspondants ont été utilisés dans des réactions croisées quantitatives chez le souriceau. Les deux agents ont une parenté immunologique, mais il existe entre eux une différence antigénique. L'auteur propose d'inclure dans un même groupe de virus les virus de la rougeole, de la maladie de Carré, et celui de la peste bovine. Des expériences, dont on donne un compte-rendu préliminaire, concernant l'antigénicité et la pathogénicité des V.R. et V.M.C. à l'égard de différentes espèces animales, ont été faites dans l'intention de rechercher les possibilités de vaccination contre la rougeole avec V.M.C. et inversement. On donne ici les premiers résultats de ces expériences.

Vergleichende Studien über Masern- und Hunde-Staupe Virus

Hunde-Staupe Virus (H.S.V.) wurde auf junge Mäuse übertragen und ein Test zum Nachweis der H.S.V.-neutralisierender Wirkung ausgearbeitet. Die Verteilung der H.S.V.-neutralisierenden Substanzen in verschiedenen Altersgruppen ist dem typischen Muster der Immunitäts-Reaktion gegen viralen Krankheiten beim Menschen ähnlich. Eine deutliche Korrelation zwischen der Anwesenheit von H.S.V.-neutralisierender Wirkung im menschlichen Serum und früher durchgegangenen Masern wurde festgestellt. Ferner wurde bei Masernkranken ein deutlicher Anstieg des H.S.V.-neutralisierenden Titers von der akuten Phase bis zur Convaleszenz erwiesen. Masern-Virus wurde auf junge Mäuse übertragen und ein Test zum Nachweis der Masern-Virus neutralisierenden Wirkung ausgearbeitet. Masern-Virus, H.S.V. und entsprechende Sera wurden für serologische Kreuz-Titrierungen bei jungen Mäusen angewandt. Dabei wurde festgestellt, dass die zwei Virusarten immunologisch verwandt sind; jedoch liess sich ein antigenischer Unterschied nachweisen. Es wird vorgeschlagen, die Viren von Masern, Hunde-Staupe und Rinderpest in eine Gruppe zusammenzuführen. Ein preliminärer Bericht wird gegeben von Versuchen über die Anti- und Pathogenität von Masern und H.S.V. bei verschiedenen Tierarten. Die Absicht war zu untersuchen, ob es möglich wäre, mit H.S.V. gegen Masern zu impfen und *vice versa*. Die preliminären Ergebnisse werden mitgeteilt.

Estudio comparativo entre los virus del sarampión y de la enfermedad del cachorro

El virus del moquillo, o mal de la joven edad del perro — canine distemper virus (C.D.V.) — fué adaptado a ratones jóvenes en lactancia y se elaboró un test para la medida de la actividad C.D.V.-neutralizadora. En el hombre, en varios grupos de edades, la distribución de las substancias C.D.V.-neutralizadoras fué hallada similar a la imagen típica de respuesta inmunitaria en las enfermedades víricas humanas. Fué hallada una relación evidente entre la presencia de actividad C.D.V.-neutralizadora, en el suero humano, y la presencia de sarampión en el pasado. Igualmente, en pacientes afectos de sarampión, hubo un significativo aumento en el título de los C.D.V.-neutralizadores de la fase aguda al período de convalecencia. El virus del sarampión — measles virus (M.V.) — fué adaptado al ratón joven y fué elaborado un test para la demostración de la actividad M.V.-neutralizadora. M.V. y C.D.V. y los correspondientes sueros antagónicos fueron usados para titulaciones serológicas cruzadas en el ratón. Ambos agentes demostraron estar inmunológicamente vinculados pero fué demostrable una diferencia antigénica. Es propuesto un grupo de virus, comprendiendo los virus del sarampión, el moquillo del perro y el virus de la "tristeza" del ganado. Se hace una comunicación preliminar de experiencias concernientes a la antigenicidad y patogenicidad de M.V. y C.D.V. en varias especies animales, siendo el propósito el de investigar la posibilidad de vacunar con C.D.C. contra el sarampión y *viceversa*. Los resultados preliminares de estas experiencias son suministrados.

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Pediatric Clinic
Karolinska sjukhu et
Stockholm 60
Sweden

Thyroid Function in Mothers of Mongoloid Infants

by J. I. EK

The cause of mongolism is not known. Some authors have suggested disease of the thyroid gland in the mother during pregnancy as a possible causal factor.

The first to suggest the possible etiologic importance of maternal hypothyroidism was Stoeltzner (1919). On inquiry into the history of 10 mothers of mongoloid children he believed to have traced symptoms of hypothyroidism during pregnancy in 3 of them. The inquiry was made by questionnaire and not by personal interview, the mothers were not examined physically and no laboratory studies were made. His publication received little attention and in 1945 he withdrew what he had written earlier and suggested instead that the use of contraceptives might be of etiologic importance.

On the basis of an inquiry among 19 mothers with mongoloid children Dollinger (1921) assailed Stoeltzner's original assumption that hypothyroidism in the mother during pregnancy might be of etiologic importance. In his material Dollinger found symptoms suggestive of hyperthyroidism to be just as common as those suggestive of hypothyroidism. Dollinger's investigation was also made simply on the basis of questionnaires.

Myers approached the problem of the possible rôle played by the thyroid gland in mongolism from another angle. Among mothers of mongoloid children he found a frequency of recognized thyroid disorders of 9 to 1, compared with a control group of the

same size and kind. From this he concluded that mongolism might be related to maternal thyroid disorders, and if so it was reasonable to expect that mongolism would occur more frequently in areas in which thyroid disorders were more common (Benda 1949).

Myers mapped out the distributions of mongoloid births and of instances of death due to diseases of the thyroid gland. He then compared the areas of the province of Ontario, Canada, which had the highest rates of thyroid disorders, with control areas. He claimed to have found significant statistical differences which supported the view that the frequency of mongolism was correlated to high thyroid morbidity.

The endocrine disorders Benda 1949 claimed to have found in mothers of mongoloid infants included also diseases of the thyroid glands. Benda said among other things: "Thyroid anomalies are so frequently seen that they are an important link in the chain of events. The common denominator is a threshold of sterility...."

Of his 50 cases in one article, as many as 10 of the mothers had thyroid deficiency, i.e. hypothyroid. One of the 50 women had a history of Grave's disease. A few other cases contained a note of "high metabolism" or "hyperactive thyroid". It thus appears that Benda (1949) regards hypothyroidism as the main characteristic of this group of women.

In textbooks and in recent literature, however (Allen & Baroff; Kurland *et al.*; Neel; Potter; Smith & Record; Öster; and others), it is still claimed that specific endo-

erine disorders in mothers of mongoloid defectives still remain to be proved.

The present investigation was prompted by the personal observation that some of the mothers of mongoloid infants had goitre. Preliminary investigation (Ek, 1957) showed that frequency of goitre was relatively high among these women. The average serum protein bound iodine was also found to be significantly higher than normal. The encouraging results of this preliminary investigation induced the author to carry out a more detailed analysis of a larger material.

Material

The material originally consisted of 64 women. Fifty-two of them were mothers of children born after 1945 and admitted to the Department of Pediatrics, University Hospital of Lund, with a diagnosis of mongolism, and 12 mothers of patients admitted for the same condition to Möllevångshemmet, Lund. All of the mothers had been living in Scania for many years.

Nine of the mothers of these patients lived so far away that it was hardly justified to ask them to present themselves for personal interview and examination. Two could not be traced. Nine mothers reported that they were unable to present themselves personally. Three of the women who were willing to cooperate were found to have been examined roentgenologically with contrast medium during the last year. Since this would probably have influenced the serum protein bound iodine level, general examination of these 3 women was postponed.

A total of 41 mothers were examined, 6 of them in their homes and the remainder at the Pediatric Department, Lund. The investigation was carried out during the years 1956-1957.

The diagnosis of mongolism could be regarded as established in all of the cases, even after critical analysis of the hospital records.

In many cases in which the child died in early age, postmortem examination had confirmed the clinical diagnosis.

The interval between the birth of the mongoloid and the present investigation was on the average 6 years. Only in one case (No. 15) was the interval as short as 6 weeks. The general appearance of the child and its later development were typical of mongolism.

Examination Procedure

Examination of the 41 probands consisted of history taking, general physical examination and determination of the serum protein bound iodine (PBI). Attempts were made to assess the general state of health by questioning the women as to any earlier hospitalization, working capacity during earlier stages of life, psychosomatic and psychoneurotic symptoms and of the frequency with which they had sought medical advice for trivial complaints. Special attention was directed to gynecologic data such as menarche, menopause, menses, any abortions or gynecologic diseases. The mothers were always questioned carefully with regard to any symptoms suggestive of hypothyroidism or hyperthyroidism.

General physical examination included auscultation of the heart, measurement of the blood pressure, palpation of the thyroid gland and examination for any stigmata of thyroid disease such as tremor, exophthalmos, pronounced dermatographism, loss of hair, puffy obesity, dry or very warm, moist skin.

Blood samples were collected from 39 probands for determination of the serum protein bound iodine. All of these women were first questioned about any medicine they had taken during the last few months and as to whether they had been examined roentgenologically during the last year.

The samples were collected with a plain-plated cannula that had been cleaned according to a special procedure for eliminating any contaminating iodine. All glassware was also cleaned in the same way. The samples were centrifuged and sent to the Isotope Laboratory, Medical Clinic, Malmö

General Hospital, for determination of the protein bound iodine (Skanse & Hedenskog, 1955).¹

The normal range for this method was determined on the basis of samples from 100 registered blood donors (50 men and 50 women in different ages) in whom clinical examination had failed to show thyroid dysfunction.

The mean value was found to be $5.9 \mu\text{g}$ per 100 ml and the standard deviation $0.7 \mu\text{g}$ per 100 ml for either sex. With a range of $M \pm 3 \sigma$ the normal limits will be $3.8 \mu\text{g}$ per 100 ml and $8.0 \mu\text{g}$ per 100 ml (Skanse & Hedenskog, 1955).

The mothers were not hospitalised. Therefore no determinations were made of the B.M.R., nor was any study with the radioisotope technique carried out.

Results

The average age of the mothers at the time of the review was 40 years. The average age at delivery of the mongoloid infant was 34 years. The youngest mothers were 18 and 19 years; the oldest were 47 years of age at the time of delivery.

Eight of the mothers were primipara and as many as 5 were above 40 years of age.

Eight of the 45 mothers had on one occasion or more been admitted earlier because of complete abortion or imminent abortion.

The average PBI value for 37 women was $7.1 \mu\text{g}/100 \text{ l}$, the standard deviation was $1.4 \mu\text{g}/100 \text{ ml}$. Despite the wide spread the difference between the mean and the normal value was highly significant ($P < 0.001$).

The PBI values in cases Nos. 18 and 32 in the table are bracketed because these patients had been operated upon for goitre,

Thanks are due to Dr. B. Skanse for the determination of the serum protein bound iodine for valuable advice.

and then the PBI is no longer a measure of their habitual thyroid function. No values are given for patient No. 3 who was pregnant, or for No. 20 who had been examined roentgenographically (cholecystography) 3 months earlier.

In Case No. 35 the patient presented a prescription for a bromium-containing medicine that she had taken a week or so earlier. The PBI was determined on two occasions in this patient and was first $7.9 \mu\text{g}/100 \text{ ml}$ and some months after she had ceased taking the medicine $8.2 \mu\text{g}/100 \text{ ml}$. The lower value is given in the tables and was used for statistical analysis.

Of the 37 cases in which the PBI was determined 6 (Nos. 8, 13, 22, 31, 36, 39) had a pathologically elevated value. Many patients showed a value approaching the upper normal limit. Only 7 had a value below the normal mean, i.e. $5.9 \mu\text{g}/100 \text{ ml}$, and in none of the 37 was the value pathologically low.

Of the 41 women who underwent a general physical examination the thyroid gland was found to be pathologically enlarged in 12. This includes the 2 who had been operated upon.

None of the patients examined were found to have any severe physical disease although 3 patients (Nos. 25, 32 and 34) had a markedly increased blood pressure and somewhat poor general health. A few abnormalities were also detected among some of the women (Nos. 13, 17 and 25).

In hardly any instance could definite clinical evidence of hyperthyroidism be found. In some of the women (Nos. 17, 25, 33, 34 and 35) in whom hyperthyroidism was suspected the blood pressure was also markedly increased (Nos. 25 and 34).

TABLE 1

No.	Age at examin. (yrs.)	Para	Abortions	Nervous- ness	Goitre	PBI	Remarks
1	21	I	0	0	+	5.8	
2	25	II	0	+	0	6.5	
3	27	II	+	0	0	—	
4	31	I	0	0	0	6.6	
5	33	III	0	0	+	6.9	
6	34	III	+	0	+	6.4	
7	35	III	0	0	0	5.1	
8	35	III	0	+	0	12.0	
9	35	III	0	0	0	7.0	
10	36	III	0	0	0	6.6	
11	37	VI	+	0	0	5.8	
12	37	I	0	+	0	7.4	
13	39	III	0	+	0	8.8	Right pupil not reactive to light
14	39	VI	0	0	0	5.7	
15	39	VI	0	0	0	6.1	
16	39	III	0	0	+	4.9	
17	40	III	0	+	0	6.6	Strabismus div. Coloboma dxt. Operated 1948. Struma atoxica
18	40	V	+	0	+	(5.6)	
19	40	IV	+	+	0	7.0	
20	40	I	+	0	0	—	
21	41	VII	0	+	0	6.0	
22	42	VI	0	+	0	10.6	
23	42	II	3	+	0	4.9	
24	42	III	0	0	+	6.6	
25	42	I	0	+	+	8.0	Mild, left-sided spastic paresis
26	42	IV	0	0	0	6.4	
27	43	I	0	0	+	8.0	
28	43	III	0	+	0	7.9	
29	43	III	0	+	0	6.5	
30	43	III	0	0	0	8.0	
31	44	III	0	+	0	8.2	
32	44	III	0	+	+	(4.5)	Operated 1951. Thyrotoxicosis
33	44	III	0	0	0	6.2	
34	45	I	0	+	+	7.9	
35	46	V	0	+	0	7.9	
36	48	II	0	+	+	8.2	
37	48	XI	0	+	0	7.1	
38	48	I	+	+	+	6.4	
39	48	II	+	+	0	9.4	
40	49	XIV	0	0	0	5.7	
41	53	VI	0	0	0	6.9	
	40					7.1	

In none of the women in whom hyperthyroidism was suspected was the PBI pathologically increased. In some cases,

however, the value bordered on the upper normal limit (Nos. 25, 34 and 35).

Some of the women appeared to be

tense and nervous. Many complained of nervous symptoms, mainly of asthenic type such as fatigue, anxiety, irritability, hypochondric complaints, heart pain without any demonstrable organic lesions and insomnia.

These general non-specific complaints which might conveniently be classified under the heading of psychoneurotic symptoms were reported more frequently by the elderly women. Only one of the women (No. 36) reported that she had spent some time in a mental hospital. One of the other mothers had been admitted earlier to a medical department, because of post-infection neurasthenia (No. 17).

The material was divided into two groups according to the presence of nervous symptoms. Group A (20 women) included those with more obvious nervous disorders. Group B consisted of the remaining 21 women with at most slight or no nervous symptoms.

The average PBI for the women in group A was 7.8 $\mu\text{g}/100\text{ ml}$, which approaches the upper normal limit.

Discussion

It is known that mongoloids are borne by mothers of a relatively high average age. The average age of mothers at the time of birth of healthy children is 29 years (Öster). In the present material the average age of the mothers at the birth of the mongoloid was about 34 years, a figure almost coinciding with that given by Öster, for example, who found an average age of 35 years.

As in earlier series (Benda; Öster; Smith & Record; Weisl), the number of p.m.parae in the present material was

relatively high, especially in the higher age classes.

It was noteworthy that goitre was found in close female relatives (mothers or sisters) in 4 cases (Nos. 6, 23, 28 and 31). Öster did not find goitre to be common among maternal female relatives of his probands, but Grave's disease was slightly over-represented.

The present material was too small to permit any conclusions about the frequency of gynecologic diseases. It should be observed, however, that the incidence of abortions among the mothers was higher than that which is found in the population in general, i.e. about 10 per cent (Beidleman; Benda; Potter).

Several cases of goitre are reported in the works of Benda. In his series of 429 mothers interviewed regarding their health Öster found that 2 had undergone thyroidectomy, 3 had goitre and 2 Grave's disease, while 2 had myxedema and 2 exogenous adiposity. Öster did not consider these findings to imply an increased thyroid morbidity. On the other hand, as mentioned, the frequency of Grave's disease was slightly, but not significantly, increased among female relatives of the mother. No such tendency was found among the paternal relatives.

Of the 41 probands, 12 (29 per cent) in the present material had a pathologically palpable thyroid gland. This figure includes the 2 who had undergone thyroidectomy (Nos. 18 and 32). The normal frequency of goitre for the female part of the population in Denmark, which is geographically similar and close to Scania, was found to be 1.1 per cent ± 0.19 per cent (Bartels).

It thus appears that the frequency of

goitre among those examined was extremely high. Since a diagnosis of goitre in the presence of only small changes may to a certain extent be subjective, it should be pointed out that at least 4 of the present women had histories of symptoms in their hospital records.

Benda's works provide abundant evidence that nervous disorders are common among mothers of mongoloids. The patients are often described as "nervous, high-strung, easily upset, depressed, fatigued". Obviously such observations must be evaluated with respect to the general stress situation in families with mongoloids.

The increased occurrence of nervous symptoms among the mothers is confirmed by Öster, who says, "many of the mothers presented nervousness and neuroses" (p. 150).

It should be stressed that in the selection of the 20 probands (group A) in the present material who were judged as having more pronounced nervous symptoms than the remainder, a certain degree of subjectivity cannot be excluded. However, the selection was made after collection of the entire material and was thus based on a comparison of the data obtained.

The probands in Group A did not differ with certainty from the remainder regarding the frequency of abortions or goitre, they did, however, tend to be older and, as will later be discussed, tended to have strikingly high PBI values.

A fairly thorough search of the literature failed to reveal reports of any examination of mothers of mongoloid children for the protein bound iodine. Investigations of mongoloids and their parents with

the use of radioisotopes have proved non-informative (Kurland *et al.*).

As mentioned, the mean value found for the PBI of all the women examined was $7.1 \mu\text{g}/100 \text{ ml}$ with a standard deviation of $1.4 \mu\text{g}/100 \text{ ml}$, which deviated significantly from a normal material ($P < 0.001$). Since the average age of the mothers of mongoloid children is unusually high, the values found were compared with those found for those controls who were 40 years of age or more. For these, the mean value was found to be $5.7 \mu\text{g}/100 \text{ ml}$ with a standard deviation of $0.6 \mu\text{g}/100 \text{ ml}$, which differed still more significantly from that of the mothers examined. As to the PBI and increasing age, it might be mentioned that on investigation of 104 overweight women Skanse & Hedenskog (1957) found no correlation between the PBI and age.

According to the literature, the PBI in a given individual is relatively constant, the variations for some healthy females being $0.5 \mu\text{g}/100 \text{ ml}$ to $0.8 \mu\text{g}/100 \text{ ml}$ and for males $0.3 \mu\text{g}/100 \text{ ml}$ to $1.1 \mu\text{g}/100 \text{ ml}$ (Danowski, Hedenburg & Greenman). Margolese & Golub, however, found a somewhat wider normal range, namely about $1.6 \mu\text{g}/100 \text{ ml}$. They also believed there was reason to suspect that the PBI showed a "cyclic rather than random" variation with a period of about 1.5 days and that the values were somewhat higher during the luteal phase and showed wider oscillations.

In the present investigation the PBI was determined on one occasion only, irrespective of the menstrual phase in which the woman happened to be. Some of the samples were collected early in the morning, others in the afternoon, etc. The

specimens were collected from the autumn of 1956 to the summer of 1957. Thus, if the PBI value tends to show any diurnal, menstrual or seasonal rhythm it will hardly have had any appreciable influence on the results obtained in the present investigation.

The mean value found for the 21 probands aged 40 years or more was $7.3 \mu\text{g}/100 \text{ ml}$ which differs but slightly from that found for the entire material, i.e. $7.1 \mu\text{g}/100 \text{ ml}$ ($0.7 > P > 0.6$). The mean found for the mothers below 40, namely $6.8 \mu\text{g}/100 \text{ ml}$, did not differ from the mean of the normal material ($M = 5.9 \mu\text{g}/100 \text{ ml}$). The age of the mother thus appears to play an important role.

The average value of 18 acceptable PBI values in Group A was $7.8 \mu\text{g}/100 \text{ ml}$, a value approaching the upper normal limit of $8 \mu\text{g}/100 \text{ ml}$. Comparison with the remaining less delicate probands in Group B with $M = 6.4 \mu\text{g}/100 \text{ ml}$ showed a significant difference ($0.01 > P > 0.001$). Since the PBI values in mothers of mongoloid defectives showed a tendency to increase with age, the values were compared with corrected control values. This comparison was based only on women who were 35 years of age or more. Even then the difference was found to be statistically significant.

In the evaluation of these findings it should be recollected that all of the women, i.e. the delicate as well as the remainder, were equally exposed to the risk of mental trauma by the birth of a mongoloid infant. Detailed analysis of the PBI values confirmed the statistical findings. Thus, all the 6 probands who had pathologically increased PBI values were in the group classified as nervous (Nos. 8, 13, 22, 31,

36 and 39). In addition, 5 of those 6 (17, 25, 29, 33, 34 and 35) in whom there was reason to suspect hyperthyroidism belonged to group A. This fact suggests that the nervous symptoms seen in the above mentioned delicate group of patients might be related to the tendency of hyperfunction of the thyroid.

It thus appears that a tendency to hyperthyroidism is a characteristic feature of many a mother of a mongoloid infant. It might, however, be mentioned that it is less likely that the normal protein bound thyroid hormone can have any influence on the development of the fetus. The protein molecule is so large that it will hardly be able to pass over into the circulation of the fetus. It is also known that normal children have been born to mothers with hypothyroidism and with hyperthyroidism (Hodges, Hamilton & Keettel; Piper & Rosen).

Investigations of the PBI in healthy pregnant women have shown a mean value at delivery of $8.18 \pm 0.23 \mu\text{g}/100 \text{ ml}$. The mean found for the control material was $6.12 \pm 0.17 \mu\text{g}/100 \text{ ml}$. The 19 new-borns examined had an average value of $6.59 \pm 0.23 \mu\text{g}/100 \text{ ml}$ which was more than $1.5 \mu\text{g}/100 \text{ ml}$ lower than that of the mothers (Friis & Secher).

With the aid of radioisotopes Grumbach & Werner have shown that the quantity of thyroid hormone transferred from the mother to the fetus may be insufficient to support normal skeletal and brain development. These authors used I^{131} labelled *L*-thyroxine or *L*-triiodothyronine which was given intravenously just before parturition.

The tendency to hyperthyroidism demonstrated in the present material of

mothers of mongoloids, is therefore probably only one of the manifestations of a more widely disturbed endocrine pattern.

In an attempt to elucidate this possibility further investigations of mothers of mongoloid children have been started.

Summary

On clinical examination of 41 unselected mothers of mongoloid infants the thyroid gland was found to be pathologically palpable in 12. Two of these women had been operated upon for toxic and non-toxic goitre. The average age of the mothers at the time of the birth of the mongoloid infant was 34 years. The average age at the time of the review was 40 years.

The mean value of the serum protein bound iodine in these women was $7.1 \mu\text{g}/100 \text{ ml}$. This differs significantly ($P < 0.001$) from the normal mean value ($M = 5.9 \mu\text{g}/100 \text{ ml}$) of women in corresponding ages from the same part of the country. In 6 women the PBI was found to be pathologically increased, i.e. more than $8 \mu\text{g}/100 \text{ ml}$. In several the value approached the upper normal limit and in none was it abnormally low.

In several cases there were striking nervous symptoms, though none of the women were in a definitely thyrotoxic state. However, the mean PBI of these women with the most striking symptoms was remarkably high, namely $7.8 \mu\text{g}/100 \text{ ml}$.

It is concluded that thyroid morbidity is abnormally high in a population of mothers of mongoloids, the tendency being towards hyperfunction of the gland.

Etude de la fonction thyroïdienne chez des femmes mères d'enfants mongoloïdes.

L'examen clinique de 41 femmes mères d'enfants mongoloïdes et prises au hasard, a révélé que la glande thyroïde était pathologiquement palpable chez 12 d'entre elles. Deux de ces personnes avaient été opérées d'un goitre toxique ou d'un goitre non toxique. L'âge moyen des mères au moment de la naissance de l'enfant mongoloïde était de 34 ans. L'âge moyen auquel elles furent examinées était de 40 ans.

Le taux moyen de l'iode fixé par les protéines du sérum chez ces personnes était de $7,1 \mu\text{g}/100 \text{ cm}^3$. Cette concentration s'écarte notablement ($P < 0,001$) du taux moyen normal que l'on observait chez les femmes du même âge dans la même région ($M = 5,9 \mu\text{g}/100 \text{ cm}^3$). Chez 6 des femmes soumises à cette étude, le taux de l'iode fixé par les protéines du sérum atteignait un niveau pathologique, c'est-à-dire qu'il était supérieur à $8 \mu\text{g}/100 \text{ cm}^3$. Dans plusieurs autres cas, il se situait à la limite supérieure de la normale. Par contre, il n'était inférieur à la normale dans aucun cas.

Bien qu'aucune de ces femmes ne se trouvât dans un état nettement thyrotoxique, des symptômes neurologiques frappants furent relevés dans plusieurs cas. Cependant, les femmes qui présentaient les symptômes les plus marquants avaient également un taux d'iode protéique remarquablement élevé de l'ordre de $7,8 \mu\text{g}/100 \text{ cm}^3$.

L'auteur en conclut que la morbidité thyroïdienne est anormalement élevée chez les mères d'enfants mongoloïdes, avec tendance à l'hyperthyroïdie.

Schilddrüsenfunktion bei Müttern mongoloider Kinder.

Bei klinischer Untersuchung von 41 auf Geräte wohl ausgewählten Müttern mongoloider Sprösslinge fand man bei 12 eine pathologisch tastbare Schilddrüse. Zwei dieser Frauen waren wegen toxischen bzw. nichttoxischen Kropfes operiert worden. Das Durchschnittsalter der Mütter zur Zeit der Geburt des mongoloiden Kindes betrug 34 Jahre. Das durchschnittliche Alter zur Zeit der Untersuchung betrug 40 Jahre.

Der Durchschnittswert des an das Serumprotein gebundenen Jodes betrug bei diesen Frauen $7,1 \mu\text{g}/100 \text{ ml}$. Der Unterschied gegenüber dem normalen Durchschnittswert ($M = 5,9 \mu\text{g}/100 \text{ ml}$), wie man ihn bei Frauen von übereinstimmendem Alter aus demselben Teil des Landes vorfindet, ist erheblich ($P < 0,001$). Bei 6 Frauen wurde ein pathologisch gesteigerter Wert des Serumproteinjodes gefunden, nämlich mehr als $8 \mu\text{g}/100 \text{ ml}$. Bei mehreren kam der Wert der oberen Grenze des normalen nahe und war bei keiner Frau abnormal niedrig.

Bei mehreren Fällen bestanden auffallende nervöse Symptome, obgleich keine der Frauen sich in einem ausgesprochenen thyreotoxischen Zustand befand. Jedoch war der durchschnittliche Serumproteinjodgehalt bei den Frauen mit den auffallendsten Symptomen ausserordentlich hoch, nämlich $7,8 \mu\text{g}/100 \text{ ml}$.

Abschliessend wird festgestellt, dass Schilddrüsenerkrankung bei Müttern mongoloider Kinder abnormal häufig sei mit einer Tendenz zur Hyperfunktion der Drüse.

La función tiroidea en madres de niños mongoloides.

A la exploración clínica de 41 madres no seleccionadas de niños mongoloides la glándula tiroidea se encontró patologicamente palpable en doce. Dos de estas mujeres habían sido operadas por bocio tóxico y atóxico. La edad media de las madres en el momento del nacimiento del niño mongoloides era de 34 años. La edad media en la época de la revisión era de 40 años.

El valor medio de la yodoproteína sérica en estas mujeres era de $7,1 \mu\text{g}/100 \text{ ml}$. Ello difiere de modo significativo ($P < 0,001$) del valor medio normal ($M = 5,9 \mu\text{g}/100 \text{ ml}$) de mujeres de edades correspondientes, de las mismas regiones. En seis mujeres la yodoproteína estaba aumentada patológicamente, es decir sus cifras eran mayores de $8 \mu\text{g}/100 \text{ ml}$. En algunas la cifra se aproximaba al límite normal superior, y en ninguna era anormalmente baja.

En algunos casos existían importantes síntomas nerviosos, aunque ninguna de las mujeres presentaba un cuadro tireotóxico definido. No obstante, el valor promedio de las yodoproteínas en estas mujeres con síntomas más acentuados era notablemente elevado ($7,8 \mu\text{g}/100 \text{ ml}$).

Se concluye en que la morbilidad tiroidea es anormalmente elevada entre las madres de los mongoloides.

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Pediatric Clinic
Lund
Sweden

Investigations on Neutralizing Antibody to Canine Distemper Virus in Human Serum from Different Countries

by P. K. HOPPER

The first observation on the remarkable presence in human serum of a substance capable of neutralizing canine distemper virus (Carré, 1905; Dunkin & Laidlaw, 1926) was made by Adams (1953). While investigating two children with primary pneumonitis, one of whom had developed acute respiratory disease after contact with a dog suffering from distemper, he demonstrated a rise in neutralizing substance to canine distemper virus in the serum of both children. This led to the important finding that adult human serum and pooled human gamma globulin frequently contained neutralizing substances to chick embryo adapted distemper virus, but that serum from young infants did not.

Further investigations were made by Imagawa *et al.* (1953, 1954) who found that the serum of some normal premature infants showed distemper neutralizing substances at a dilution of 1/20, and that certain specimens of adult serum could neutralize virus to as high a titre as serum from ferrets which had been artificially immunized against the disease.

Observations were then made in the S.A. on the incidence of the neutralizing

substance by Karzon (1955), who demonstrated that the factor was heat stable, and had all the properties of an antibody. It was also found to disappear from the serum by the 6th month and to reappear later, reaching an incidence of almost 100 % in adult serum. Later Carlström (1956) working in Sweden, showed that antibody was present in the serum of most children over 6 years of age, but was seldom present in children less than 4 years old.

Two questions arise: Is the antibody due to contact with distemper infected dogs? Is it due to an antigenic overlap between measles and distemper viruses, as suggested by Adams & Imagawa (1957*b*.).

With the intention of throwing light on these matters, specimens have been obtained from various countries with very different dog populations, and the present study describes comparative observations on these sera.

Materials and Methods

Neutralization tests.—Two-fold dilutions of serum ranging from undiluted serum to a dilution of 1/80 were mixed with an

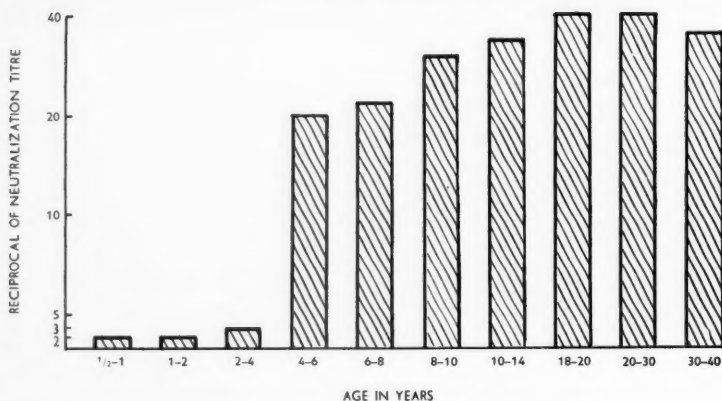


Fig. 1. Titres of canine distemper neutralizing antibody in pools of normal human sera from different age groups in the population of the United Kingdom.

equal volume of virus and held at 20° (room temperature) for 60 minutes. 0.1 ml of each mixture containing 50 ID₅₀ of virus was then inoculated on to the chorio-allantoic membranes of 7-8 day old chick embryos using the method of Beveridge & Burnet (1946). 4-7 eggs were used for each dilution and they were then incubated at 36-37°. After 7 days' incubation the membranes were removed and examined for the presence or absence of lesions, the 50% neutralization endpoint being calculated by the method of Reed & Muench (1938). 50 ID₅₀ of distemper virus was arbitrarily selected for the test, as this was the smallest convenient amount which gave uniformly satisfactory lesions on individual control membranes.

Virus.—The strain used was an egg-adapted strain¹ which had been passaged many times on the chorio-allantoic membrane of eggs, and which was completely non-virulent to dogs and ferrets. Pools of virus were stored at -76°.

Titration of virus.—0.1 ml amounts of decimal dilutions of virus were inoculated on to the chorio-allantoic membrane of eggs as described above, and the 50% infectivity end-point determined after 7 days incubation. As has been found by others, the linear coalescent lesions which were invariably present made the customary poek-counting method of titration inapplicable.

Sera.—The majority of sera were from normal individuals, but some were obtained from patients with non-infective orthopaedic disabilities. All sera were stored at -10°, and were inactivated undiluted at 56° for 30 min. before use.

Experimental Results

Normal human sera obtained from different parts of the U.K. were first investigated and were pooled in groups of 15-25 specimens. The ages investigated extended from 6 months to 40 years, and in the case of children between the ages of 2 and 14.

¹ Kindly supplied by Mr. A. B. MacIntyre, Wellcome Research Labs., Beckenham, Kent.

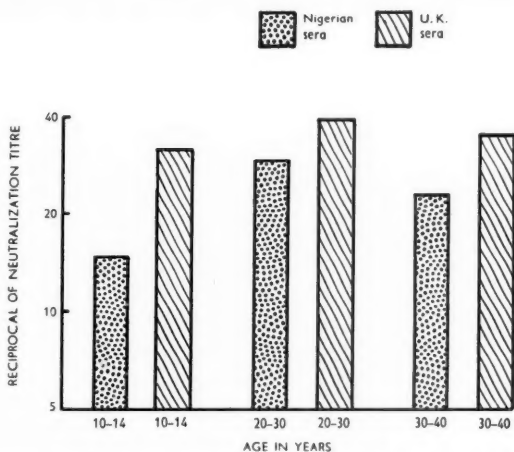


Fig. 2. Neutralization titres to canine distemper virus in pooled normal human sera from Nigeria, compared with U.K. sera.

10 years; each pool of serum covered an age range of 24 months. The results of neutralization tests against egg-adapted canine distemper virus for each of the age groups are shown in Fig. 1. No antibody could be detected in undiluted sera from infants aged 6 months up to the 2nd birthday. This is shown as a level of less than $1/2$, as all titres refer to the final dilution of serum in the reacting serum-virus mixture, and not to the dilution of serum added. It will be seen that the level of distemper neutralizing antibody rises sharply from the age of 4 years, and reaches a maximum of $1/40$ at the age of 18-20 years, or possibly earlier. (Insufficient sera were available to form a pool for the age group 15-18 years.) After remaining at a similar level for the age group 20-30 years, the titre of the next 10 year group fell a little, to a level of $1/35$.

Sera obtained from groups of children and adults in Lagos, Nigeria, are shown in Fig. 2 in comparison with U.K. sera.

Children aged 10-14 years show a titre of only $1/15$ as against a level of $1/33$ in U.K. children. Adults aged 20-30 and 30-40 years also show lower antibody levels than in English sera, and a drop in antibody titre is again apparent after the age of 30 years, the level falling from $1/30$ to $1/23$.

To obtain as great a contrast as possible, sera were next examined from children in Iceland where the dog population was deliberately reduced to negligible proportions a few years ago, following a serious spread of hydatid disease to humans. Levels of distemper antibody in pooled serum from two groups of children aged 6-8 and 8-10 years living in Reykjavik, the capital of Iceland, are shown in Fig. 3. Although the number of dogs in towns is now very small indeed, and it is doubtful if any cases of distemper have occurred in the past 13 years, the level of antibody present is already $1/16$ at the age of 6-8 years, and it rises to a higher level by the

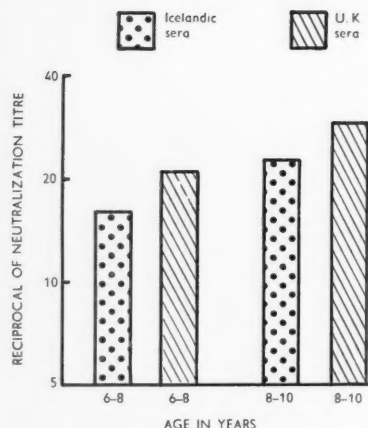


Fig. 3. Titres of distemper neutralizing antibody in pools of normal human sera from Iceland, compared with U.K. sera.

age of 8-10 years. Both levels are nevertheless lower than in U.K. sera of the same age groups.

The significance of these antibody levels in relation to age is a very interesting point as until recently, apart from one epidemic period the yearly incidence of measles in Iceland has been very low, the figures for 6 of the 8 years up to 1946 ranging between 0 and 23 cases (W.H.O. Report 1952). In 1947, however,—the year when the older of these Icelandic children were born—a big epidemic occurred, and since then the annual incidence of the disease has risen enormously, outbreaks of varying size occurring in all but one of the following 7 years.

A further comparison has also been made against sera from adults living in Russia. A pool of 27 sera from young adults aged 18-20 years living near Leningrad where it is reported that there are hardly any dogs, showed a titre of 1/46. This level of antibody is slightly higher

than the level in the corresponding age group in England (1/40).

No previous work has been done on the levels of distemper antibodies at various ages in children and adults, using pools of sera from different countries, but some comparison with published work can be made in regard to the age at which neutralizing antibody first appears. By screening sera at a constant dilution, Karzon (1955) demonstrated that very few children aged 6-20 months in New York State, U.S.A., had any antibody, but that by 20-36 months 42% of them showed individual levels of 1/5 or more. Carlström's findings for children in Stockholm, Sweden (Carlström 1956) showed that positive sera were seldom present in children less than 4 years old, but that about half were positive in the age group 4-6 years.

The findings described here with U.K. sera where a sharp rise in antibody occurs in the age group 4-6 years, and little is present before this age, lie closely in line with results reported from Sweden. In both these countries the appearance of neutralizing antibody occurs rather later in infancy than in the United States.

Discussion

The earliest suggestion that the virus of canine distemper might be related to human disease was made by Bryan (1928), who described respiratory illnesses in 11 children exposed to animals suffering from this disease. Further observations were made by Nicollé (1931), Vuori (1936) and Whitney (1943), but the total evidence including that from Adams (1953) still remained far too inconclusive to establish any definite causal relationship between

overt human disease and contact with the virus.

The presence in human sera of antibody which neutralizes the virus of canine distemper appears to be confined to serum from human beings and rhesus monkeys (Karzon, 1955), the sera from horses, calves, fowls, rabbits, and other animals being quite negative. The common occurrence of this antibody in human serum from countries as far apart as the arctic and equatorial zones, suggests that its appearance is due to contact with a very ubiquitous agent or group of agents of bacterial or more likely viral nature. Its similar incidence in areas where dogs are scarce, makes it very improbable that its presence is simply due to contact with infected dogs, and an explanation of its occurrence must be sought along other lines.

In an endeavour to exclude the existence of antibody on the basis of an immunological relationship with other viruses, Karzon (1955) tested distemper against poliomyelitis, influenza, herpes and lymphocytic choriomeningitis viruses, but found no cross-neutralization. Similarly, in a study of patients' histories, no relationship was apparent between the presence of distemper antibody and a history of measles, rubella and other infectious diseases. A correlation between a history of measles and the presence of distemper antibodies was however found by Carlström (1957), in a study of 116 children aged between 6 months and 15 years, and she also demonstrated a rise in distemper antibody in paired sera from measles patients. Further laboratory evidence of an immunological relationship between measles and distemper viruses is also avail-

able (Imagawa & Adams, 1957; Adams & Imagawa, 1957*b*).

The epidemiological information given here on the levels of distemper neutralizing antibody in sera from various countries, is in line with an antigenic relationship to an agent of such world-wide prevalence. Especially noteworthy is the absence of distemper antibody from sera in the first few years of life after disappearance of maternally derived antibody, followed by sharply rising levels in childhood beginning at the age when measles is most common. After early adulthood a fall in distemper antibody level takes place, this happening at a time when measles infection is seldom known to occur.

The observation that with the exception of dogs the only animals found to contain distemper antibodies in their serum are monkeys is a significant finding, as the monkey is a species in which measles antibodies are known to occur frequently and from which viruses immunologically related to measles can be recovered (Ruckle, 1956).

Apart from cases of respiratory disease due to measles in which no rash occurs, viruses related to measles have now been isolated from patients with giant-cell pneumonia (Enders, 1957). It is also possible that on closer analysis strains of other viruses may be found to show minor degrees of antigenic cross-reaction with distemper. In the absence of isolation of distemper virus from human material, demonstration of neutralizing antibody to this virus in persons suffering from respiratory disease and in contact with dogs ill with distemper, is not sufficient information to incriminate this virus as the etiological agent. Despite the similar histo-

logical findings between canine distemper in animals and certain respiratory diseases in children (Adams *et al.*, 1956; Adams & Imagawa, 1957*a*), there is as yet no definite evidence that the virus of distemper is at all pathogenic to man.

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Summary

Human sera from normal individuals in the U.K. aged between 6 months and 40 years have been investigated for the presence of neutralizing antibody to egg-adapted canine distemper virus. Practically no antibody was present under 4 years, but after this age levels rose rapidly, a high titre was reached by the age of 18–20 years and maintained for a further decade.

Sera from Iceland and parts of Russia where dogs are extremely infrequent gave results generally similar to those found in U.K. sera. The results are compared with serological findings from other countries, and the significance of antibody discussed in the light of recent evidence of an immunological relationship between distemper and measles viruses.

Recherches sur un anticorps antagoniste du virus de la maladie des chiens dans des échantillons de sérum humain provenant de différents pays.

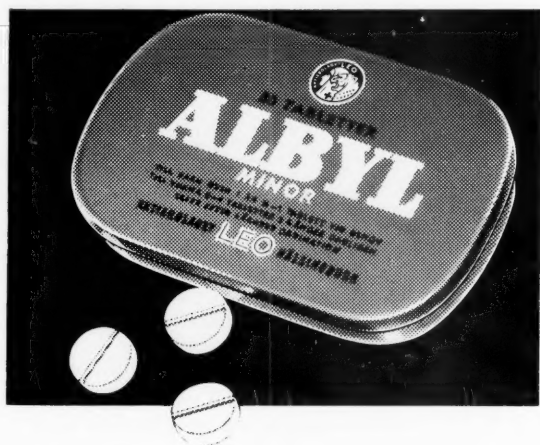
Des échantillons de sérum humain prélevés dans le Royaume Uni sur des individus normaux âgés de 6 mois à 40 ans ont été examinés au point de vue de la présence de l'anticorps neutralisant le virus de la maladie des chiens cultivé sur œuf. Le taux de cet anticorps était pratiquement nul avant l'âge de quatre ans, mais à partir de cet âge, on a constaté qu'il s'élevait rapidement pour atteindre vers l'âge de 18 à 20 ans un niveau élevé et s'y maintenir durant une dizaine d'années. Les échantillons de sérum prélevés en Islande et dans certaines régions de la Russie où les chiens sont extrêmement rares ont donné des résultats généralement comparables à ceux enregistrés pour les échantillons de sérum prélevés en Grande-Bretagne. L'auteur a comparé ces résultats avec ceux qui avaient été obtenus au point de vue sérologique dans d'autres pays et il examine le rôle que peut jouer cet anticorps à la lumière des constatations récentes qui ont été faites à propos des relations immunologiques qui paraissent exister entre le virus de la maladie des chiens et celui de la rougeole.

Untersuchungen über Hundestaupevirus neutralisierenden Antikörper in menschlichen Seren aus verschiedenen Ländern.

Menschliche Seren von normalen Individuen in Grossbritannien im Alter von 6 Monaten bis zu 40 Jahren wurden auf die Gegenwart von eiadaptiertes Hundestaupevirus neutralisierendem Antikörper untersucht. Vor dem Alter von 4 Jahren war praktisch kein Antikörper vorhanden, aber nach diesem Alter stieg der Antikörperspiegel rasch an und bei 18–20 Jahren wurde ein hoher Titer erreicht und für eine weitere Dekade beibehalten.

Seren aus Island und Teilen von Russland, wo Hunde ausserordentlich selten sind, ergaben im allgemeinen ähnliche Resultate wie Seren aus Grossbritannien. Die Ergebnisse werden mit serologischen Befunden aus anderen Ländern verglichen und die Bedeutung des Antikörpers wird im Licht der neueren Nachweise einer immunologischen Verwandtschaft zwischen Staupe- und Masernvirus erörtert.

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INDIKATIONER:

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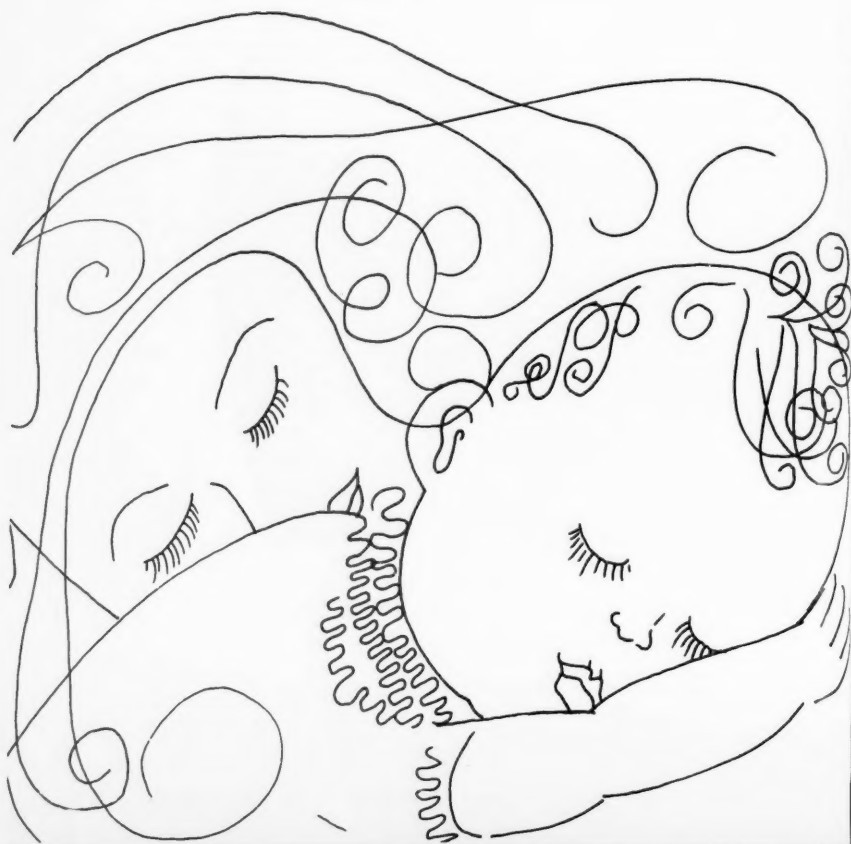
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AKTIEBOLAGET **LEO** HÄLSINGBORG



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Priset på Findus Tilläggsvälling varierar mellan kr. 3:05 och 3:90 per burk, beroende på vilken marginal som tillämpas inom handeln. *Kostnaden per liter färdig välling blir då storleksordningen kr. 0:92—1:18.*

Ingredienser: Fettfri torrmjöl, laktos, vetemjöl, vegetabiliskt fett, sackaros, mineralämnen och vitaminer.

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Proteinhalt:

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Fetthalt:

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Vitamin B ₂	1,2 mg	0,8 mg
Niacin	5,6 mg	5 mg
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Investigaciones sobre un anticuerpo neutralizante al virus del moquillo canino en suero humano de diferentes países.

Se ha investigado la presencia de un anticuerpo neutralizante al virus del moquillo del perro adaptado al embrión de pollo en sueros humanos procedentes de individuos normales de la Gran Bretaña con edades comprendidas entre los seis meses y los cuarenta años. Prácticamente no se observó la presencia de anticuerpo por debajo de los cuatro años, pero después de esta edad sus niveles aumentan rápidamente; la mayor titulación se obtuvo a la edad de 18-20 años, manteniéndose para la siguiente década. Los sueros procedentes de Islandia y regiones de Rusia, donde los perros son extremadamente raros, dieron resultados generalmente similares a los obtenidos con sueros de Gran Bretaña. Los resultados se comparan con las observaciones serológicas de otros países, discutiéndose la significación del anticuerpo en relación con las recientes observaciones de un nexo inmunológico entre el moquillo y el virus del sarampión.

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National Institute for Medical Research
Mill Hill
London, N. W. 7
England.

Ingested Fat in Relation to Serum Lipids in Coeliac Disease

by BERTIL LINDQUIST and STURE RAFSTEDT

A decreased intake of fat has been stated to be the most important factor affecting the level of serum lipids in man. However, during recent years several investigative results have been produced showing that vegetable fats have a depressing effect on the serum lipids even when the fat content remains high (Groen *et al.* 1952, Kinsell *et al.* 1952). Ahrens *et al.* (1955) found corn oil particularly effective in lowering serum cholesterol. They suggested that the effect of dietary fats on the serum cholesterol level in man depends on the relative degree of saturation of their constituent fatty acids. Since the polyunsaturated fatty acid content of vegetable fat (principally linoleic acid) is high, attention was logically directed toward the influence of the essential fatty acids *per se* upon the serum cholesterol level. Sinclair (1956) came to the conclusion that diets deficient in essential fatty acids give hypercholesterolemia, while diets rich in these fatty acids lower the serum cholesterol level. Bronte-Stewart *et al.* (1956) showed in experiments on human volunteers that animal fats gave a prompt rise of serum cholesterol but the same amount of vegetable fat (olive oil) gave a prompt fall. Highly un-

saturated animal oils such as seal oil and pilchard oil had cholesterol-lowering effects similar to those obtained with vegetable oils, while hydrogenated vegetable fat and saturated fractions of vegetable and fish oils caused a rise in serum cholesterol level. Beveridge *et al.* (1956) found in an investigation of 35 human beings that a corn oil diet decreased the serum cholesterol from 220 to 160 mg per 100 ml, i.e. 32 per cent. When butter fat or lard was then given the serum cholesterol increased significantly. In 40 volunteers a fat-free diet for 8 days gave a decrease of serum cholesterol from 200 to 150 mg per 100 ml. When corn oil was then given the serum cholesterol level was still further decreased. In an extensive study of the influence of a corn oil diet on the serum lipids in human volunteers Malmros & Wiegand (1957) found the same lowering effect.

Although the mechanism of the effect of vegetable oils on the serum lipids is still obscure, the fact remains that diets containing appreciable quantities of such oils lower the serum cholesterol levels in a reproducible manner by 20 to 30 per cent.

It is generally agreed in coeliac disease

that the fat depots and the serum lipids are depleted as in prolonged starvation, and that the defective absorption of fat is the cause of the low serum lipid values. In recent years it has been shown that in this disorder the gluten protein has a harmful effect on the intestinal fat absorption (van de Kamer *et al.* 1953). It has also been found that in coeliac disease fat containing a large proportion of diunsaturated fatty acids is better absorbed than fat mainly composed of saturated fatty acids (Borgström & Lindquist 1957). We therefore found reason to investigate the effect of different kinds of fat on the serum lipids in coeliac disease. When the fat was supplied in form of corn oil, the serum lipids were at a significantly lower level than when the fat was given as cream. The results are especially significant against the background of the different degree of absorption from the digestive tract of the two kinds of fat supplied, corn oil fat being absorbed to a much higher degree (Borgström & Lindquist *l.c.*).

Experimental

The *experimental series* comprised three children—two normal subjects (Cases 1 and 2), and one case of coeliac disease (Case 3), see Case Histories below.

Experimental diets. Two formulae with the same content of protein and carbohydrate but containing different kinds of fat were used. In one of them fat was given in the form of corn-oil ("corn oil formula"), and in the other as cream ("cream formula"). The composition which originally was described by Ahrens *et al.* (1954), is given in Table 1. In both formulae the calorie content was 1.25 cal. per g, the distribution of calories being 15 per cent protein, 40 per cent fat and 45 per cent carbohydrates.

Diet periods. In the two normal subjects (Cases 1 and 2) both formulae were given for a period of about 2 weeks to each child. The total daily volume, which for both formulae amounted to about 1000 g, was distributed over 4-5 meals. Beside the formulae the subjects received during the experimental periods vegetables, juice, lemonade and fruits. Adequate amounts of vitamins were also given. The child with coeliac disease (Case 3) was studied for 8 different periods, see Table 2 (for details about the diet com-

TABLE 1. *Composition of formulae supplied.*

Diet formulae and ingredients	Weight (g)	Protein (g)	Fat (g)	Carbohydrate (g)
<i>Cream formula</i>				
Milk	100	3.3	4.0	5.0
Cream, 40%	45	1.0	18.0	1.6
Skimmed milk powder	29	14.5	0.3	11.3
Dextrose	38	—	—	38.0
Water	188	—	—	—
Total	400	18.8	22.3	55.9
<i>Corn oil formula</i>				
Corn oil	21.9	—	21.9	—
Skimmed milk powder	37.5	18.8	0.4	14.7
Dextrose	41.5	—	—	41.5
Water	299	—	—	—
Total	400	18.8	22.3	56.2

position during these periods, see Borgström & Lindquist l.c.).

Analytic methods. All the blood samples in this investigation were taken in the post-absorptive state, i.e. in the morning before the first meal. The children had then been fasting for at least 8 hours.

Capillary blood was collected from the tip of a finger. After retraction of the clot the blood was centrifuged and the serum pipetted off. A quantity of 0.6 ml serum was sufficient for the performance of the following determinations:

1. Determinations of total lipids (Swahn 1952, 1953).
2. Determination of the relative concentrations of lipids in electrophoretically separated lipoprotein fractions (Swahn 1952, 1953).
3. Determination of total and free cholesterol (Schoenheimer & Sperry 1934).
4. Determination of lipid phosphorus (Rafstedt 1955).

Case Histories

Case 1 (Normal child).—The child was a boy, aged 6½ years, and weighed 21,400 g. He was the fifth of six siblings. Both parents were healthy. He had always received a normal diet. There had never been any abnormal stools or signs of disturbances of

the fat metabolism. At the time of investigation he was under observation in the clinic for enuresis nocturna. It was found by roentgenography that he had a cystic malformation of the urinary bladder. In all other respects he was found to be healthy.

Case 2 (Normal child).—The patient was a boy, aged 3 10/12 years, and weighed 15,700 g. He was the second child of healthy parents. He had received a normal diet, and there had been no disturbances from the gastrointestinal tract. He was admitted to the clinic on account of a swollen knee, the etiology of which was found to be of traumatic origin.

*Case 3 (Coeliac disease).*¹—The patient was a boy, aged 6½ years and weighed 16,800 g. He was the seventh child of healthy parents. One sister died at one month of age from unknown cause. All the other siblings were alive and healthy. Since about 8 months of age there had off and on, especially during infections of the respiratory tract, been voluminous and greyish stools. The abdomen had always been large and prominent, and especially during the last two years this had troubled him fairly much. Apart from restriction of fat he had received a normal diet.

On admission he was pale and emaciated, especially the arms and legs. He was somewhat small for his age (length 108 cm). He had an anemia with a red-cell count of 3.3 millions and a hemoglobin percentage of 41.

TABLE 2. *Experimental periods studied in Case 3.*

Diet period	Kind of fat ²	Fat intake	Fat absorption	
		Daily (g)	Daily (g)	% of intake
1. (Ordinary food)	cream	58	40	68
2. (Corn oil formula)	corn oil	82	74	91
3. (Cream formula)	cream	57	44	76
4. (Corn oil formula)	corn oil	76	71	92
5. (Corn oil formula + food, rich in gluten)	corn oil	64	55	86
6. (Ordinary food, poor in gluten)	cream	37	32	86
7. (Ordinary food, rich in gluten)	cream	56	40	72
8. (Corn oil formula + food, rich in gluten)	cream + corn oil	66	56	85

¹ A more detailed description of the clinical history of this case is given by Borgström & Lindquist l.c. (Case 3).

² In Periods 1 and 6–8 the fat was, in addition to cream, also given in the form of milk and butter.

The glucose tolerance test showed a low and prolonged curve. Beside ordinary treatment the patient was given in the clinic different diet combinations (see Table 2). During Period 2, when corn oil formula was given, a marked improvement of his general condition was noted, the abdominal distention decreased and the appearance of the faeces improved to normal colour and consistency.

Results

Total lipids and lipoprotein fractions

These values are given in Figs. 1 and 2. In the two normal subjects (Fig. 1) the values of the total lipids as well as of the α - and β -fractions lay within normal limits during both the experimental periods (cf. Rafstedt 1955). In none of these patients

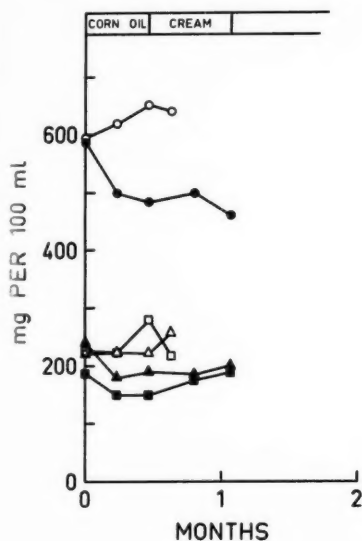


Fig. 1. Serum values of total lipids and lipoprotein fractions in two normal children on corn oil formula and cream formula diets. Case 1 (open symbols): boy, age 6½ years, weight 21.4 kg; Case 2 (solid symbols): boy, age 3 10/12 years, weight 15.7 kg. (Symbols see Fig. 2.)

were the levels of the total lipids and the β -fraction found to change to such a degree to give a significant difference between the values of the corn oil formula period as compared to those of the cream formula period. The differences observed were not greater than those seen in successive determinations in one and the same subject when a uniform diet is given. The same is to be said about the α -fraction, which in the normal subjects was not either influenced by changes in the diet.

In Fig. 2 the values of the total lipids and the lipoprotein fractions are presented for the patient with coeliac disease. In this figure are also given the values of the fat absorption for the different experimental periods (these values are taken from Borgström & Lindquist l.c.) The following results of the determinations of the total lipids and lipoprotein fractions were obtained:

On admission the values for the total lipids and β -lipoproteins were somewhat low, namely 379 and 197 mg per 100 ml, respectively. These values are probably referred to the diet poor in fat which the patient received at home. Even the α -fraction showed values below normal limits. Inadvertantly no analyses of the serum lipids were carried out for the first period with cream fat.

During Period 2, when the fat was given in form of corn oil with a daily absorption not less than 75 g, the values were somewhat lower than on admission. Thus the mean values were for the total lipids 339 and for the β -fraction 152 mg per 100 ml.

During Period 3, when the fat was given as cream, there was a marked rise of the total lipids and of the β -fraction in spite of the fact that the daily amount of fat

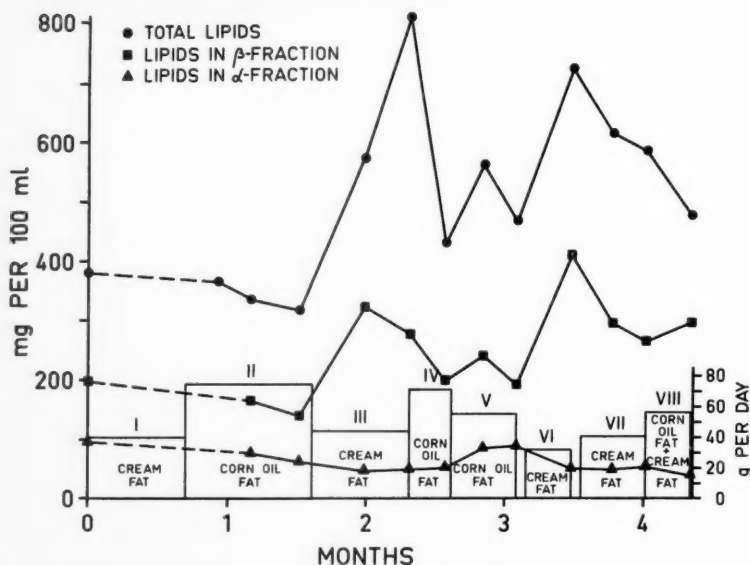


Fig. 2. Serum values of total lipids and lipoprotein fractions in one case of coeliac disease on various diets containing fat either as corn oil or as cream fat. The columns represent the average daily amount of absorbed fat for each period. Case 3: boy, age 6½ years, weight 16.8 kg.

absorbed was about 45 per cent less than during the preceding period, the mean values of the two determinations for this period being 693 and 299 mg per 100 ml, respectively. The values of the α -fraction showed a slight drop.

During *Period 4 and 5*, when the fat again was given in form of *corn oil*, there was a marked decrease of the values of the total lipids and the β -fraction, the mean determinations for the above-mentioned periods being 487 and 210 mg per 100 ml, respectively. Furthermore, it should be noted that the amount of absorbed fat per day was higher than during *Period 3*; during *Period 4* this amounted to about 70 g daily as compared to 43 g during *Period 3*. During *Period 4 and 5* there was also a slight increase in the values of the α -fraction.

During *Periods 6 och 7*, when the fat was given in form of *cream*, there was again a marked rise in the values of the total lipids and the β -fraction, the mean of the determinations for these two periods being 644 and 323 mg per 100 ml, respectively. It should be noted that during these two periods the amount of absorbed fat per day was about 30 per cent lower than during the two preceding periods. A slight decrease was also observed in the α -fraction.

During *Period 8* the fat was given to about two thirds as *corn oil* and one third as *cream*. From the next preceding values there was a moderate decrease of the total lipids to a value of 477, and an increase of the β -fraction to a value of 296 per 100 ml. Only one determination was, however, carried out for this period.

Fig. 1. Lipid values in serum of a patient with coeliac disease. The symbols represent the following: Total lipids (solid line with circles), Lipids in β -fraction (solid line with squares), Lipids in α -fraction (dashed line with triangles).

The values of the total lipids and the β -fraction were higher than during the two preceding periods. A slight decrease was also observed in the α -fraction.

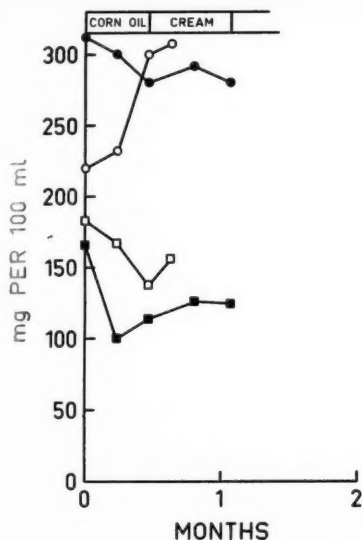


Fig. 3. Serum values of cholesterol and phospholipids in two normal children on corn oil formula and cream formula diets. Case 1 (open symbols): boy, age 6½ years, weight 21.4 kg; Case 2 (solid symbols): boy, age 3 10/12 years, weight 15.7 kg. (Symbols see Fig. 4.)

Cholesterol and phospholipids

These values are presented in Figs. 4 and 5. In the two normal subjects the values of the total cholesterol as well as of the phospholipids lay within normal limits during both the experimental periods (Wamberg 1954, Rafstedt 1955). The values of the total cholesterol were, however, somewhat low during the corn oil period as compared to the initial values on admission. When fat then was given in form of cream the values again increased to a moderate degree. The phospholipids showed no significant alterations.

In Fig. 5 are given the values of the total cholesterol and phospholipids for the patient with coeliac disease, and in the same figure are also presented the values of the fat absorption during the different experimental periods. For these periods (except Period 1, see above) the following results were obtained:

During *Period 2*, when fat was given as *corn oil*, the mean values of the cholesterol and phospholipids were 77 and 121 mg per 100 ml, respectively. Both the values are within normal limits.

During *Period 3*, when fat was given as *cream*, there was a significant rise of both cholesterol and phospholipids in spite of the fact that the daily amount of fat absorbed was about 45 per cent less than during the preceding period, the mean values being 115 and 180 mg per 100 ml, respectively.

During *Periods 4 and 5*, when the fat again was supplied in form of *corn oil*, there was an insignificant drop of the cholesterol value to a mean of 106, and a decrease of the phospholipids to a mean value of 139 mg per 100 ml.

During *Periods 6 and 7*, when *cream* fat was given, there was again a rise in the cholesterol and phospholipids, the mean values being 176 and 193 mg per 100 ml, respectively.

During *Period 8*, when the fat was given both as *cream* and as *corn oil* the cholesterol value decreased to 115 mg per 100 ml, while the value of the phospholipids was approximately the same as the next preceding value. Only one determination was, however, carried out for this period.

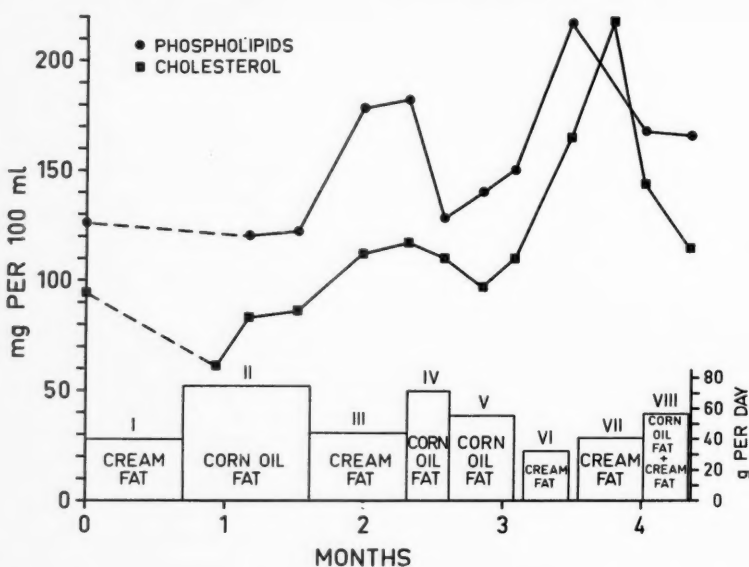


Fig. 4. Serum values of cholesterol and phospholipids in one case of coeliac disease on various diets containing fat either as corn oil or as cream fat. The columns represent the average daily amount of absorbed fat for each period. Case 3: boy, age $6\frac{1}{2}$ years, weight 16.8 kg.

Discussion

The alterations of the serum lipids observed in the two normal children were only referred to the total cholesterol values. The decrease of the cholesterol values during the corn oil period was marked in one of the subjects and moderate in the other. Even in normal adults given a corn oil diet a significant decrease is observed only in the total cholesterol values, the other serum lipid components showing no marked changes. Malmros & Wiegand (1957) found in normal adults that the decrease of the total serum cholesterol was only slight or moderate when the initial value was less than 200 mg per 100 ml. The higher the initial total cholesterol value, however, the more pronounced was the decrease found during the corn oil diet.

In the patient with coeliac disease it is of a considerable interest to note the marked alterations of the serum lipids when the dietary fat was shifted from corn oil to cream. At the first of these shiftings there was an increase of the total lipids as well as of the β -fraction by about 100 per cent, and at the second an increase by 33 and 54 per cent, respectively. Concerning the total cholesterol and the phospholipids there was a rise of 50 per cent at the first shifting, and a rise of 65 and 40 per cent, respectively, at the second. Thus the changes of the serum lipids, brought about by alteration of the dietary fat from corn oil to cream were considerably greater in the patient with coeliac disease than in the normal subjects. As compared to the findings of Malmros &

TABLE 3. *Component fatty acid in corn oil and cream fat.*

The figures given are per cent of total fatty acids.

Fatty acid	Corn oil	Cream fat
C ₈ -C ₁₂	—	12.5-19
Myristic	—	5 -14
Palmitic	7.7	25 -35
Stearic	3.5	10 -15
Oleic	45.4	20 -30
Linoleic	40.9	0.5- 2
Arachidonic	0.4	—

Wiegand (l.c.) this is remarkable because the serum lipids in the coeliac patient were relatively low.

It is difficult to explain the marked rise of the serum lipids when the dietary fat is supplied in form of cream, but obviously this is related to the fatty acid composition, cream fat containing more saturated and less essential fatty acids than corn oil (Table 3) (Baugeman & Jamieson 1921). An explanation may be suggested according to Sinclair (1956). He considers that serum cholesterol is normally esterified mainly by polyunsaturated fatty acids. When the body is deficient in these acids, cholesterol tends to esterify with the endogenously manufactured saturated fatty acids. Such esters are "abnormal" and may accumulate in the blood resulting in increased cholesterol values in the serum. A diet high in saturated fat increases the body's requirement for essential fatty acids. Hence a high animal fat intake, when low in essential fatty acids, may induce a conditional essential fatty acid deficiency. Deficiency states are characterized by biochemical or anatomic lesions,

which can usually be reversed when the specific nutrient lacking is made available to the body and effectively utilized. The marked increase of the serum lipids—except the α -fraction—brought about by the cream fat in the present case (Case 3) would now be explained by assuming a greater requirement of unsaturated fatty acids in coeliac disease as compared to normal conditions. The closer cause of this is, however, unknown. It should also be born in mind that there probably are several other factors that may influence the serum lipids in man.

It is to be noted that when the coeliac patient had been given the corn oil diet for a long time, and the stools were normal and the nutritional status good, the serum lipid values were within normal limits except for the α -fraction. During the whole time of observation the values of the α -lipoproteins were below normal limits, although they showed a slight tendency to increase when corn oil formula was given. It would therefore be of interest to follow patients with coeliac disease fed corn oil fat during still longer periods in order to see if all the serum lipid components are changed to normal values, and, furthermore, if the response to different fat diets then is altered. Perhaps in this way it will be possible to get a better understanding of the relationship between the nutritional status of the body with respect to essential fatty acids, and the level of the serum lipids.

Summary

Against the background of the disturbed fat absorption the effect of different kinds of fat on the serum lipids was investigated in one patient with coeliac disease. In addition two normal children were studied. The subjects were given a liquid formula feeding

containing fat either as corn oil or as cream. Fat represented 40 per cent of the total calorie supply.

When the dietary fat was shifted from corn oil to cream a considerable elevation of all of the serum lipids components—except the α -fraction—was observed in the coeliac child in spite of a marked decrease in the absolute amount of absorbed fat. In the normal subjects the shifting of the dietary fat was reflected only in the total cholesterol values, the difference, however, being much less than that found in the coeliac child.

The different effects of the two kinds of fat on the serum lipids are discussed with reference to the fatty acid composition of the fat supplied.

Rapport entre les graisses ingerées et la concentration des lipides dans le sérum en cas de maladie coeliaque.

Sur le tableau de fond de la perturbation de la résorption des graisses, les auteurs ont étudié l'influence de l'ingestion de différentes espèces de graisses sur la concentration des lipides du sérum chez un sujet atteint de maladie coeliaque. En même temps, deux enfants normaux furent également soumis à l'expérience. Ces sujets reçurent des aliments liquides renfermant des graisses soit sous forme d'huile de maïs soit sous forme de crème. Ces graisses représentaient quarante pour cent du total de l'apport de calories. Le remplacement de l'huile de maïs par la crème fut suivi d'une augmentation considérable du taux de tous les lipides du sérum — à l'exception de la fraction alpha — chez l'enfant atteint de maladie coelique et cela malgré une diminution marquée de la quantité absolue de graisses résorbées. Chez les sujets normaux, le changement de régime se traduisit uniquement par une modification du taux de cholestérol total, mais la différence fut bien moins forte que celle qui avait été observée chez l'enfant atteint de maladie coeliaque. Les auteurs commentent les différences des effets de ces deux espèces de graisses sur la concentration des lipides du sérum et les mettent en rapport avec la composition de ces graisses en ce qui concerne les acides gras.

Fettverdauung und Serumlipide bei Coeliakie.

Mit der Störung der Fettresorption im Hintergrund des Krankheitsbildes wurde der Einfluss verschiedener Fette auf die Serumlipide bei einem Patienten mit Herter'scher Krankheit untersucht. Überdies wurden zwei normale Kinder auf dieselbe Weise studiert. Die Untersuchungspersonen erhielten eine flüssige Diät, die Fett entweder in der Form von Maisöl oder Sahne enthielt. Fett stellte 40 % der gesamten Kalorienzufuhr dar. Wenn man sich in der Fettverabreichung vom Maisöl auf die Sahne umstellte, wurde eine erhebliche Erhöhung aller Serumlipidkomponenten — mit Ausnahme der Alphafraktion — bei dem mit der Krankheit behafteten Kinde beobachtet, trotz der merklichen Abnahme der absoluten Menge des resorbierten Fettes. Bei den normalen Untersuchungspersonen spiegelte sich die Umstellung in der Fettverabreichung nur im Verhalten der Gesamtcholesterinwerte wieder, wobei der Unterschied viel kleiner ausfiel als bei dem kranken Kind. Der Unterschied im Einfluss der beiden Fettarten auf die Serumlipide wird unter Berücksichtigung der in der Zusammensetzung des verabreichten Fettes Anteil nehmenden Fettsäuren besprochen.

Relación de la grasa ingerida con los lípidos séricos en la enfermedad celiaca.

En relación con las alteraciones de la absorción grasa se estudió el efecto de diferentes tipos de grasa sobre los lípidos séricos en un paciente con enfermedad celiaca. Además se estudiaron dos niños normales. Se administró a los pacientes una alimentación líquida que contenía grasa bien en forma de aceite de cereales o de nata. La grasa representaba el 40 % del aporte calórico total. Cuando la grasa de la dieta se cambió de aceite vegetal a nata se observó en el niño celiaco una considerable elevación de todos los componentes lipídicos del suero (excepto la fracción alfa), a pesar de una marcada disminución de la cantidad absoluta de grasa absorbida. En los sujetos normales la variación de la grasa de la dieta se reflejó únicamente en las cifras totales de colesteroína, la diferencia, no obstante, fué mucho menor que la observada en el niño celiaco. Se discuten los diferentes efectos de los dos tipos de grasa sobre los lípidos séricos en relación con la composición acidograsa de la grasa administrada.

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University Pediatric Clinic
Barnsjukhuset
Göteborg (B.L.)

Pediatric Clinic
University of Lund
Lund, Sweden (S.R.)

From the Institute for the Care of Mother and Child, Prague, Podoli
(Director: Prof. J. Trapl, M.D.)

Acidosis and Anaerobiosis in Full Term Infants

by BOHUMIR VEDRA

In 1916 Ylppö first described the so-called acidotic constitution of the newborn. This finding was repeatedly confirmed in the following years on the basis of a low alkaline reserve both in cord blood and during the early postnatal period. Relative acidosis was confirmed in foetal cord blood as compared with maternal blood by all authors who measured blood pH directly, both postnatally (Bell *et al.*, 1928; Siedentopf & Eisner, 1929; Eastman, 1931; Noguchi, 1937; Beer, Bartels & Raczkowski, 1955), as well as before the onset of labour (Kaiser, 1953).

The metabolic character of newborn acidosis was shown by the high levels of organic acids in cord blood (Bell *et al.*, 1928) and the increased excretion of these after birth (György *et al.*, 1928; Räihä, 1941).

The origin of this metabolic acidosis has not been explained. Räihä first advanced the theory in 1941 that there may be a partial anaerobiosis in the foetus and newborn. According to this theory, the foetus, even under physiologic conditions suffers from a relative lack of oxygen in utero, as manifested by the high concentration of lactic acid in the cord blood. This has been supported by a number of

sources, even though it has not been unequivocally demonstrated (Wilson *et al.*, 1948; Smith, 1951; Brock, 1954; Österlund, 1955; Beer *et al.*, 1955).

The question of whether the foetus utilizes anaerobic metabolic pathways also in the presence of adequate oxygen supply is not only of great theoretical importance, but has also a great practical importance from the point of view of prevention and therapy of intrauterine asphyxia. This communication examines the above theory in mature, normal newborns. It has been assumed here, as a working hypothesis, that metabolic acidosis of the normal newborn is not of foetal origin, but of maternal, not a manifestation of partial anaerobiosis of the foetus but of the diffusion of acid metabolites from the mother to the foetus. It may be expected that the greater the accumulation of such metabolites in the maternal circulation during labour, the greater both the maternal and foetal acidosis.

Methods

It is not feasible to follow the dynamics of acid-base balance in the prenatal foetus, and the development of the metabolic acidosis can consequently not be observed.

It has been assumed that if foetal metabolic acidosis is a function of maternal acidosis they should be correlated to each other. Lactic acid concentration should be higher in maternal than in foetal blood.

The following methods have been used:

(1) Plasma bicarbonate by the Van Slyke method; (2) blood pH by means of a Radiometer 3 (Copenhagen) glass electrode system (measured at 23°C); (3) lactic acid in the blood by the method of Baker & Summerson, 1941.

Maternal blood for analysis was withdrawn from the antecubital vein, foetal blood from the cord as soon as this was available for manipulation.

The accuracy of the methods was checked by numerous parallel measurements, and the following standard errors were found: plasma HCO_3 (98 analyses), 0.26 vol.%; lactic acid (94 analyses), 1.51 mg%; pH, 0.01 unit (52 analyses).

Other statistical methods were the same as used by Österlund (1955). In testing the significance of differences the usual Student's *t*-test was used. The errors of the differences between means were calculated with due regard to the fact that the variables compared were correlated.

Results

(a) The relationship of plasma HCO_3 in mother and foetus

In all, 34 primiparae and 32 multiparae were followed. Average values are shown in Table 1.

It appears from Table 1 that plasma HCO_3 in the foetus is higher than the maternal levels at the moment of birth, the differences being at the level of significance 0.001.

TABLE 1. *The relationship of plasma HCO_3 in mother and foetus.*

	Number	Average (vol. %)	S.D.
Primiparae	34 mothers	40.21 ± 0.75	4.38
	34 newborns	44.99 ± 0.72	4.23
	Difference	4.78 ± 0.44	
Multiparae	32 mothers	43.09 ± 0.69	3.91
	32 newborns	47.08 ± 0.68	3.90
	Difference	3.99 ± 0.17	

The relationship between individual pairs of mother/foetus values shows a close relationship (Fig. 1).

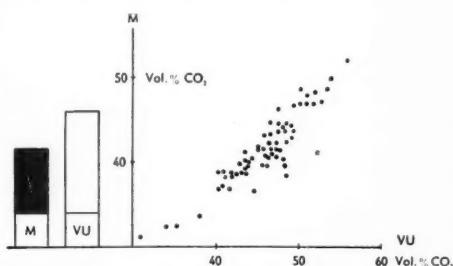


Fig. 1. Correlation between plasma bicarbonate of the mother (M) and newborn (VU).

The correlation coefficient (*r*) for primiparae is 0.82, for multiparae 0.97.

(b) The relationship of blood pH in mother and foetus

Thirteen pairs of subjects were investigated. Average values are given in Table 2.

TABLE 2. *The relationship of blood pH in mother and foetus.*

	Number	Average	S.D.
Mothers	13	7.48 ± 0.015	0.055
Newborns	13	7.46 ± 0.017	0.063
Difference		0.02 ± 0.01	

It can be seen from Table 2 that cord blood pH in the umbilical vein of active newborns is lower than maternal venous blood. The difference is not significant.

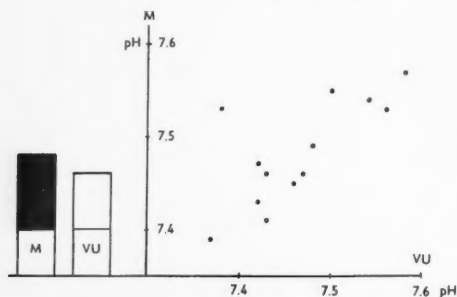


Fig. 2. Correlation between blood pH in mother and newborn.

The relationship between individual pairs of results are shown in Fig. 2, showing a close relationship (r is 0.71).

(c) *The relationship between blood lactic acid concentrations in mother and newborn*

Fourteen primiparae and fourteen multiparae were followed. Average values are presented in Table 3. It appears from this table that lactic acid concentrations at the moment of birth are higher in maternal blood than in newborns. The difference in primiparae is at the level of significance 0.01, while the difference in multiparae is not significant.

TABLE 3. *The relationship between lactic acid levels in the blood of mother and fetus.*

	Number	Average (mg %)	S.D.
Primiparae	Mothers 14	47.52 ± 4.2	15.09
	Newborns 14	39.73 ± 4.2	15.04
	Difference	7.79 ± 1.96	
Multiparae	Mothers 14	37.32 ± 5.7	20.6
	Newborns 14	33.12 ± 3.8	13.6
	Difference	4.20 ± 2.7	

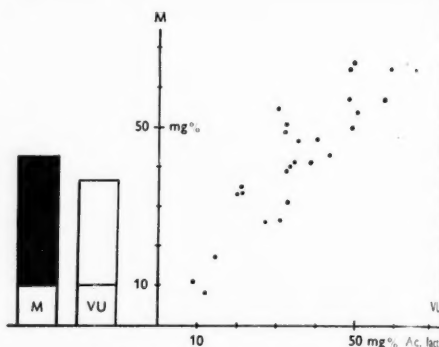


Fig. 3. Correlation between lactic acid concentrations in mother and newborn.

The relationship between individual pairs of values are shown in Fig. 3, from which a close relationship may be seen. In primiparae r is 0.89, in multiparae 0.92.

(d) *Plasma bicarbonate in the umbilical artery and vein*

Thirty samples of cord blood were examined. Average values are shown in Table 4. Venous plasma bicarbonate is

TABLE 4. *Plasma bicarbonate in the umbilical artery and vein.*

	Number	Average (vol. %)	S.D.
Artery	30	51.86 ± 0.7	3.9
Vein	30	50.32 ± 0.7	4.0
Difference		1.54 ± 0.2	

significantly higher than arterial in the cord. The difference is at the level of significance 0.001.

(e) *Lactic acid in umbilical artery and vein*

Forty-seven active newborns were investigated. Average values are given in Table 5. It can be seen that blood lactic

TABLE 5. *Lactic acid in arterial and venous blood in the cord.*

	Number	Average (mg %)	S.D.
Vein	47	36.33 ± 0.03	13.8
Artery	47	37.60 ± 2.07	14.1
Difference		1.27 ± 0.55	

acid levels are lower in the umbilical vein than in the artery by about 1.27 mg %. The difference is at the level of significance 0.05. If we take into consideration that the error of the method is 1.51 mg %, the difference must be very carefully interpreted.

On the basis of Figs. 1 to 3 it can be stated that acid-base balance in the mother and foetus are in direct relationship. It would appear that they mutually interact. Because lactic acid is higher in maternal blood than in the foetus, it can be concluded that an increasing lactic acid concentration in the mother produces an increase in the foetus.

Discussion

In the foetus the low bicarbonate and pH of cord blood is taken to be the result

of lactic acid accumulation. It has been generally assumed that this high lactic acid level originates in the partial anaerobic metabolism of the foetus. This theory is widely accepted at the present even though not absolutely proven (Wilson *et al.*, 1948; Reardon *et al.*, 1950; Smith, 1951; Brock, 1954; Österlund, 1955; Beer *et al.*, 1955). The theory of foetal partial anaerobiosis is primarily based upon the following data:

1. Oxygen tension available for oxygenating cord blood in the placenta is about at the level of the atmosphere at the top of Mt. Everest. Since such an O_2 tension is not sufficient for the adult, it is assumed that it is also insufficient for the foetus in utero, and this concept has found its way into obstetrics as so-called physiological hypoxia.

Haselhorst (1954) has argued against such a concept, stating that normal, natural foetal conditions cannot be considered to be "hypoxic".

2. The second basic support of the theory of partial anaerobiosis consists of Bell's data (Bell *et al.*, 1928) on lactic acid

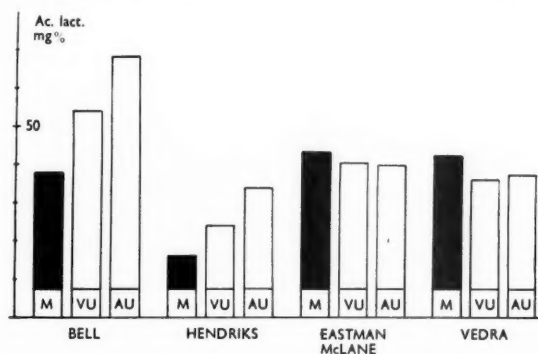


Fig. 4. Lactic acid levels in blood from the maternal antecubital vein (M), umbilical artery (AU) and umbilical vein (VU) according to Bell *et al.* (1928), Eastman & McLane (1932), Hendricks (1957) and the author, in comparison.

concentrations in mother and foetus. According to Bell this latter acid is twice as concentrated in the foetus as in the maternal body fluids. Hendricks (1957) also supports this ratio, giving values of 16.20 mg % for maternal blood and 34.07 mg % in cord blood after spontaneous birth (maternal specimens were drawn 2 to 19 min. before birth).

Eastman & McLane (1932) however found opposite ratios for lactic acid.

Fig. 4 shows the relationship of lactic acid concentrations in maternal and cord blood (umbilical vein) according to Bell *et al.* (14 samples), Eastman & McLane (9 samples), Hendricks (15 samples) and our own values (28 samples).

3. According to Bell *et al.*, lactic acid concentration in the umbilical artery is about 15 mg % higher than in the umbilical vein (15 samples), a finding in agreement with the theory of partial anaerobiosis, showing an endogenous, foetal origin. Hendricks (19 observations) has maintained that lactic acid concentration is significantly higher in the umbilical artery (34.07 mg %) than in the umbilical vein (24.78 mg %).

Eastman & McLane reported, however, that lactic acid concentration is the same on both sides of the cord circulation (11 measurements). This is in agreement with our own results (47 measurements, see Table 5).

The author of the theory of partial anaerobiosis (Räihä, 1954) himself admits that the A-V difference across the cord for both lactic and pyruvic acids is insignificant and cannot influence foetal metabolism.

4. Pyruvic acid in the umbilical artery is higher (1.57 mg %) than in the

vein (1.29 mg %) according to Räihä, 1954.

5. It has been shown that premature infants are usually in more severe acidosis than mature newborns (Reardon *et al.*, 1950; Wilson *et al.*, 1948; Branning, 1942). Räihä explains this finding in terms of anaerobic metabolism. Were this true it might be expected that organic acid concentration in the blood of premature infants should be higher than in full term infants. Räihä (1941) has measured this variable and has found in mature infants values from 3 to 18 mM/l (average from 18 samples 5.7), and in premature infants from 1 to 10 mM/l (average from 28 samples 4.4) in the first hour of extra-uterine life, i.e. full term infants had higher levels than prematures.

It has been here found that in some premature infants a direct relationship exists between the lactic acid concentration in maternal and cord blood, of the same order as in full term infants, maternal levels being higher than foetal (Vedra & Ulrych, preliminary communication).

From this review it appears that the theory of partial foetal anaerobiosis has a number of weaknesses. The following two facts appear clear:

1. Lactic acid levels in cord blood are raised (Bell *et al.* 1928; Eastman & McLane, 1932; Hendricks, 1957; our own data).

2. The foetus has a greater degree of acidosis than the mother (Bell *et al.*, 1928; Siedentopf & Eissner, 1929; Eastman, 1931; Noguchi, 1937; Beer *et al.*, 1935; Kaiser, 1953; our own data).

The origin of the raised lactic acid levels in cord blood is crucial for the above theory. There are 2 or 3 possibilities: first,

a foetal origin, second, a maternal origin, third, a mixed origin.

Hendricks' data from simultaneous samples from mother and foetus during Caesarian section, but before the onset of labour, show a higher level of lactic acid in foetal blood (umbilical artery, 23.12 mg %, umbilical vein, 16.27 mg %, maternal 12.3 mg %). This suggests that part of the source of the lactic acid may be the foetus.

Eastman & McLane, on the other hand, in one case of Caesarian section before the onset of labour, have recorded the following levels: maternal venous 19.4, umbilical vein 16.7 and umbilical artery 16.6 mg %.

In the material presented above there is one such case, a diabetic mother, where the duplicate analyses were: maternal venous 33.7 (33.3), umbilical vein 20.3 (20.3) and umbilical artery 16.1 (14.6) mg %.

Hendricks' results after spontaneous delivery differ strikingly from our own, despite the fact that the same chemical methods were used.

It is often assumed that maternal and foetal conditions a few minutes after birth are the same as just before birth. This assumption may not hold for lactic acid

concentration since this latter parameter rises sharply during the latter stages of labour, reaching a maximum just at or after the mother's muscular effort at the end of the second stage (see Fig. 5). There remain one or two contractions unassisted by maternal pressure, i.e. there may be an interval of 2-5 min. before the umbilicus presents. Such short time intervals can, in the case of lactic acid, make a great difference in blood concentrations and diffusion gradients.

It is here suggested that when maternal lactic acid concentration rises, the diffusion gradient is from the mother to the umbilical vein, and that when the maternal concentration falls, this gradient can reverse.

The relatively higher maternal lactic acid concentration, the lower (though elevated) foetal levels, and the close correlation between the two, suggest a diffusion of this organic acid from the mother to the foetus. Certainly the rise in maternal lactic acid concentration during labour (Bockelman, 1927; Siedentopf, 1932; Winkler & Hebeler, 1939; Hodr, Štembera & Herzmann, personal communication; our own data) leads to rise in foetal concentrations.

The relatively lower newborn and foetal serum pH's remain to be explained. It appears that this acidosis cannot be of purely metabolic origin, since the foetus is more acidotic despite a lower lactic acid level. This could be produced by a high $p\text{CO}_2$, i.e. the acidosis of the foetus would be a combination of metabolic (foetal and or maternal origin) and foetal respiratory acidosis.

Plasma bicarbonate in the foetus at the moment of birth is higher than in the

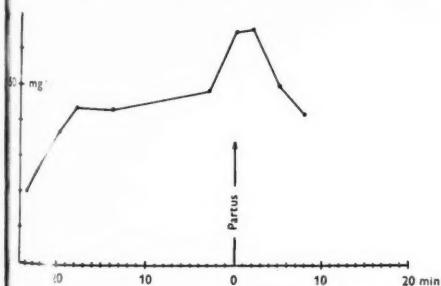


Fig. 5. Lactic acid concentration during labor.

mother. This is true for every paired set of measurements. This same effect has been reported by Hallman *et al.* (1954), Österlund (1955) and others, in the human, Roos & Romijn (1938) in the cow, Keys (1934) in the goat, and Young (1952) in the rabbit.

Bell *et al.* (1928), Malfatti & Burtscher (1930), Beer *et al.* (1955) have found the opposite relation in regard to bicarbonate and suppose a lower foetal alkaline reserve to be due to a higher foetal lactic acid concentration.

Of more importance is the constant, close correlation between foetal and maternal values, with a highly significant correlation coefficient, as Österlund (1954-1955) first pointed out, and as Young (1952) has observed in the rabbit.

The same linear correlation can be seen for serum pH in Fig. 3. Similar correlation can be drawn from data presented by Siedentopf & Eissner (1929).

Our own observations, as well as those of other authors, indicate that all three indices of acid-base balance in mother and newborn (bicarbonate, pH and lactic acid) show a close correlation, thus suggesting some form of interaction. Since maternal lactic acid concentration is higher than foetal, it is suggested that the rise in this parameter during labour produces a concentration rise in the foetus. The question remains as to whether this change is brought about by a diffusion

process alone, and whether endogenous foetal lactic acid production (if any) can be regarded as an adaptation to a "physiological" oxygen lack.

Plasma bicarbonate was significantly lower in the umbilical vein than in the artery in our material. Our results are in agreement with those of Österlund (1955), but not in agreement with the data of Beer *et al.* (1955). According to the latter authors foetal alkaline reserve is increased by about 1 vol. % of CO₂ with a placental circuit, suggesting to these authors that the foetus transfers acid metabolites to the mother. These authors base their work on that of Bell *et al.* (1928): a fall in lactic acid concentration across the placenta of about 15 mg % represents an equivalent rise in alkaline reserve of 1 vol. %. These authors see in this a specific adaptation of the foetal organism to an insufficiency of O₂: anaerobic production of lactic acid, transfer of this in the placenta to the maternal circulation, thus improving the physiological range of the haemoglobin dissociation curve. Unfortunately, these authors did not measure lactic acid themselves, and the results presented in the present communication are not in agreement with this concept.

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Summary

A detailed criticism of the theory of partial anaerobiosis in the normal newborn has been presented. The correlation between several indicators of acid-base balance in the mother and foetus at the moment of birth has been studied, and the following relationships have been found:

(1) Maternal plasma bicarbonate at the moment of birth is lower, and pH and lactic acid concentration higher, than the corresponding values in the foetus.

(2) There was a direct relationship between plasma bicarbonate, blood pH and lactic acid concentration in mother and foetus.

(3) Umbilical venous bicarbonate was lower than in the umbilical artery.

(4) There was no significant A—V difference in lactic acid concentration across the placenta at birth.

It would appear from these results that acid-base balance of the newborn is dependent on acid-base balance of the mother, the close correlation indicating a high degree of interaction. It is suggested that the raised level of lactic acid after spontaneous birth is probably of mixed foetal and maternal origin.

It would appear from the relative concentrations of lactic acid in mother and foetus that, rather than serving as evidence for partial anaerobiosis in the foetus, there is a diffusion gradient for this substance from the maternal to the foetal circulation. This point has not been directly proved, but the fact that a rise in maternal levels during labour is followed by a rise in foetal levels is highly suggestive.

Acidose et anaérobiose chez les nourrissons nés à terme.

On a présenté une critique détaillée de la théorie de l'anaérobiose partielle chez le nouveau-né normal. La corrélation entre plusieurs indicateurs de l'équilibre de l'acide de base a été étudiée chez la mère et le foetus au moment de la naissance, et les rapports suivants ont été trouvés :

1. La teneur en bicarbonate du plasma maternel, au moment de la naissance, est plus basse, et le pH et la concentration de l'acide lactique sont plus élevées que les valeurs correspondantes chez le foetus.

2. Il y avait un rapport direct entre le bicarbonate du plasma, le pH du sang et la concentration de l'acide lactique chez la mère et le foetus.

3. La teneur en bicarbonate dans les veines ombilicales était plus basse que celle dans les artères ombilicales.

4. Il n'y avait pas de différence importante A—V dans la concentration de l'acide lactique à travers le placenta à la naissance.

Il semblerait de ces résultats que l'équilibre de la base d'acide du nouveau-né dépend de l'équilibre de la base d'acide de la mère, la corrélation étroite indiquant une interaction élevée. On suggère que le taux élevé de l'acide lactique après accouchement spontané est probablement d'origine, à la fois, foetale et maternelle.

Il apparaîtrait d'après les concentrations en question de l'acide lactique chez la mère et le foetus qu'il y a une diffusion graduelle de cette substance de la circulation maternelle à celle du foetus, plutôt que de prendre ceci comme preuve d'une anaérobiose partielle chez le foetus. Ce point n'a pas été directement prouvé, mais le fait qu'une augmentation dans les taux maternels pendant l'accouchement est suivie d'une augmentation dans les taux du foetus est très significatif.

Acidosis und Anaerobiosis bei vollentwickelten Kindern.

Eine eingehende kritische Betrachtung der Theorie betreffend partielle Anaerobiosis bei normalen Neugeborenen wurde gegeben. Die Beziehung zwischen einzelnen Indikatoren des Säure-Basen-Gleichgewichtes bei Mutter und Fötus im Moment der Geburt wurden studiert. Es konnten folgende Beziehungen aufgestellt werden:

Der Plasma-Bikarbonat-Spiegel der Mutter im Moment der Geburt ist niedriger, der pH-Wert und die Milchsäurekonzentration höher, verglichen mit den entsprechenden Werten beim Fötus.

Es bestand eine direkte Beziehung zwischen Plasma-Bikarbonat, pH-Wert des Blutes und der Milchsäure-Konzentration bei Mutter und Fötus.

3. Der Bikarbonatspiegel in der Umbilikalvene war niedriger im Vergleich zur Umbilikalarterie.

4. Es zeigte sich kein signifikanter arterio-venöser Unterschied betreffend die Milchsäurekonzentration in der Placenta bei der Geburt.

Aus diesen Versuchen würde sich ergeben, dass das Säure-Basen-Gleichgewicht des Neugeborenen abhängig ist vom Säure-Basen-Gleichgewicht der Mutter; die enge Beziehung zeigt eine hochgradige Wechselwirkung an. Es ist naheliegend anzunehmen, dass der nach spontaner Geburt erhaltene Milchsäurewert sich wahrscheinlich aus fötalem und mütterlichen Komponenten zusammensetzt und somit gemischten Ursprungs ist.

Es ist auf Grund der voneinander abhängigen Milchsäurekonzentrationen bei Mutter und Fötus deutlich, dass hier eher eine Diffusionsneigung dieser Substanz vom mütterlichen zum fötalen Kreislauf besteht als sie als ein Beweis für eine partielle Anaerobiosis beim Fötus zu betrachten. Dieser Punkt wurde nicht direkt bewiesen, aber die Tatsache, dass ein Ansteigen der mütterlichen Werte sub partu seinerseits ein Anwachsen der fötalen Werte zur Folge hat, liegt sehr nahe.

Acidosis y anaerobiosis en los niños a término.

Ha sido expuesta una crítica detallada de la teoría de la anaerobiosis parcial del recién nacido normal. Se han estudiado las correlaciones entre diversos indicadores del equilibrio ácido-base en la madre y en el feto en el momento del parto, habiéndose hallado las relaciones siguientes.

1. El bicarbonato plasmático materno era más bajo, en el momento del parto, y el pH y la concentración de ácido láctico más elevadas que los valores correspondientes del feto.

2. Existía una relación directa entre el bicarbonato del plasma, el pH sanguíneo y la concentración de ácido láctico en la madre y en el feto.

3. No existía ninguna diferencia A - V significativa en la concentración de ácido láctico de la placenta en el momento del parto.

4. El bicarbonato era más bajo en la vena umbilical que en la arteria umbilical.

De estos resultados puede inferirse que el equilibrio ácido-base del recién nacido depende del equilibrio ácido-base de la madre; sus íntimas correlaciones demuestran una gran interacción. Se sugiere que el aumento de ácido láctico después del parto espontáneo es probablemente de origen mixto, materno-fetal.

La concentración relativa de ácido láctico en la madre y en el feto inducen a pensar que, mas que demostrar una anaerobiosis parcial en el feto, indican la existencia de un gradiente de difusión para esta substancia de la circulación materna a la fetal. Ello no se ha comprobado directamente, pero es muy sugestivo el hecho de que el aumento de la tasa materna durante el parto vaya seguido de una disminución de los valores de ácido láctico en el feto.

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Institute for the Care of
Mother and Child
Prague-Podoli
Tjekoslovakia

CASE REPORT

Marfan's Syndrome Associated with Hearing Defect

Report of a Case in One of a Pair of Twins

by G. EVERBERG

From the Frederiksberg Hospital, Copenhagen, E.N.T. Department. (Director: F. Norsk, M.D.)

Marfan's syndrome is generally taken to mean *arachnodactyly* ("spider fingers") with *ectopia lentis* and in some cases also *congenital heart disease*. Marfan described the first case in 1896, but his patient had only the first-mentioned sign. Now, about 350 cases are said to be on record (McKusick, 1956). The great majority (204) are included in a monography by Rados from 1942.

The full syndrome consists, briefly, of: *Skeletal deformities*: Arachnodactyly, kyphosis, scoliosis, pigeon breast, flatfeet, hammer toe, dolicocephaly, and high-arched palate. *Soft-tissue abnormalities*: Scanty subcutaneous tissue, hypotonic muscles, laxity of joints, ligaments, and cartilage. Thus, "bat ears" are commonly present. *Defects of organs*: Ectopia lentis, anomaly of the lungs (sub-normal number of lobes), and congenital heart disease. As a rule, the intelligence is normal.

Formerly, patients with severe forms of this syndrome usually succumbed to pneumonia, partly owing to their thoracic and pulmonary deformity, and partly due to their asthenic habitus. Sudden death due to dissecting aneurysm of the aorta and other cardiovascular lesions has been reported by Etter (1943), Goyette & Palmer (1953), Whit-

taker & Sheemann (1954), McKusick (1956), and Wilson (1957).

Case Report

The patient is an 11-year-old girl. She is a dizygotic twin, born in breech presentation, birth weight 1750 g. During infancy she had several attacks of pneumonia treated with penicillin. She had also had all the ordinary childhood ailments. At the age of 4, she had been admitted to the department where the present examination took place. At that time, the diagnosis was adenoid vegetations and acute, recurrent tonsillitis; adeno-tonsillectomy was performed. No abnormality of body build or of the appearance of hands and feet was noted then. It was stated that 4 months prior to the first admission she had had a mild, bilateral middle ear infection which rapidly yielded to penicillin. At the time of the first admission, the otoscopic findings had been normal.

When she reached school age, it was noticed that her gait became strange, and her feet had grown abnormally long and narrow. Orthopedic examination revealed severe flatfeet which were treated with inner soles, and from then on she always had to have shoes made to measure. Gradually, she grew at an abnormally rapid rate, getting thin and lanky. Her schoolmates constantly



Fig. 1. The patient and her twin brother.

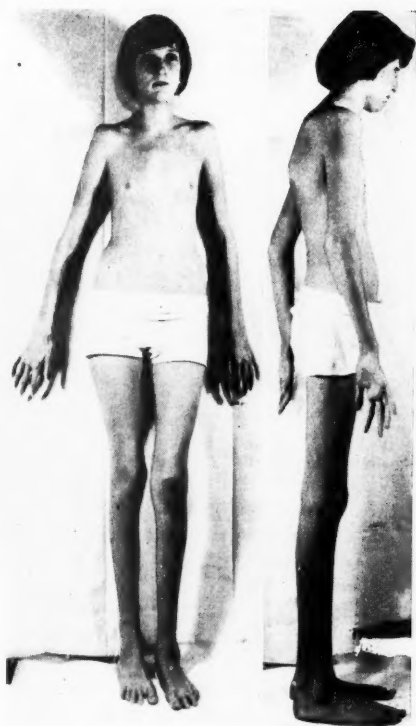


Fig. 2. The propositus.

teased her, calling her "the Eiffel tower" and the like. Otherwise, she did well at school, and her intelligence had always appeared to be normal. At the age of 9 she had to consult an ophthalmologist (Dr. Blegvad) who diagnosed: "Bilateral ectopia lentis, arachnodaetly".

On Oct. 23, 1957 she was admitted to the E.N.T. Department of the Frederiksborg Hospital with right-sided otitis. For 2 months she had had discharge from the right ear which had not exhibited any abnormality since the middle ear infection at the age of 4. On physical examination her height was found to be 170 cm and her weight 40.3 kg. Her normal twin brother was then 150 cm tall and weighed 39 kg. The patient was extremely thin with very long, thin limbs and under-developed, hypotonic muscles.

Hands and feet were abnormally long and narrow, and so were the fingers and toes; there was pronounced laxity of the joints. In addition, pronounced flatfeet (Figs. 1, 2 and 3). She also exhibited pigeon breast and winged scapulae as well as dolicocephaly and a high-arched palate. Her intelligence appeared to be entirely normal. No syphilitic stigmata. Otoscopy revealed on the right a polyp, almost as large as a pea. After its removal, there was a dry defect in Shrapnell's membrane, and the ear disease quickly subsided. No abnormality on the left. X-rays of the temporal bones showed on the right inhibited pneumatization, but no destructions; left side normal. The external ears were of normal position and normal shape. The hearing was perceptibly impaired on the right (cf. audiogram Fig. 4), the side of



Fig. 3. Note the abnormal laxity of the joints.

the otitis. This impairment was partly of the conduction type, due to the otitis, but as is apparent from the inclination of the curve towards the high tones, there was also some perceptive impairment. The latter was also present on the left. The "practical hearing" was slightly impaired: She could hear whispered voice at a distance of 3-4 m on the right and at 5-6 m on the left. The perception of ordinary spoken voice was almost normal on the left (10-12 m) and slightly

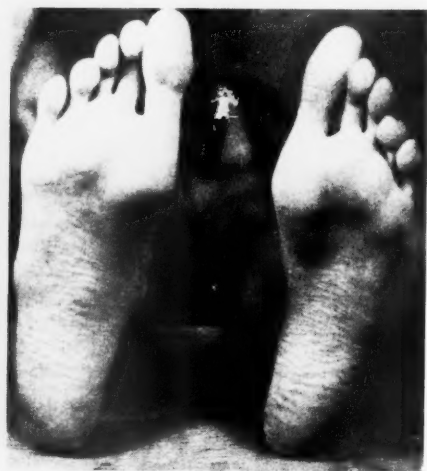


Fig. 4. Note the abnormal length of the feet and the marked flatfootedness.

reduced on the right (5-6 m). Vestibular examination revealed normal findings in the rotation test (caloric vestibular test was omitted, as the defect on the tympanic membrane had become dry).

Ophthalmic findings: Vision in Rey $< 5/6$, vision in L. eye, $< 6/9 - 6/6$ with own correction. Ophthalmoscopy following instillation of homatropine showed the lens dislocated slightly upwards and nasally on both sides. Its lower margin with the delicate suspensory fibres was visible. The patient was advised not to take part in physical exercises, not to dive into the water, etc., as this might lead to a rupture of the fibres.

Medical examination (including ECG and X-rays of the chest) with a special view to possible heart diseases, showed no definite abnormality.

Neurological examination (including EEG) showed no abnormality.

Laboratory tests: No abnormality on testing the urine for albumin, blood, sugar, and pus. Haemoglobin 91%, E.S.R. 3 mm/hr, B.P. 105/65. W.R. negative. In a *skin biopsy* the collagen bundles showed signs of marked degeneration.

The patient's next-of-kin, i.e. parents and two siblings, were examined by the author. They did not exhibit any signs of arachno-

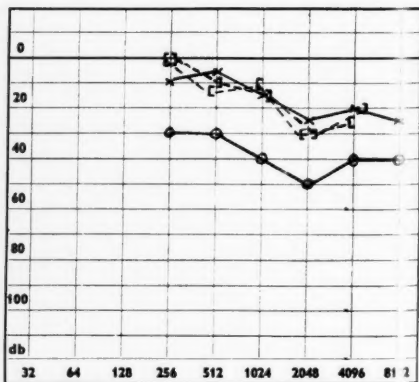


Fig. 5. Patient's audiogram. O—O, right ear, air conduction; X—X, left ear, air conduction; ---, [right ear, bone conduction;]---], left ear, bone conduction.

dactly and had no ophthalmic complaints. In height they ranged from 163 to 176 cm. Her father and elder brother had left-sided chronic otitis with a corresponding conduction deafness on the affected side, but no perceptive deafness. Her twin brother was normal in every respect, in body build as well as ophthalmologically and otologically. Ophthalmoscopy showed no signs of ectopia lentis, and audiometry revealed completely normal hearing, particularly no signs of perceptive hearing loss.

In addition, data regarding height, weight, characteristics of body build, structural defects of the eyes, and hardness of hearing in the paternal and maternal aunts and uncles and their children, a total of 14 individuals were collected by questionnaires. According to the replies (which were returned by all but one) they did not exhibit any abnormalities. A male cousin on the paternal side reported hearing impairment "due to constant discharge". Otological examination revealed a bilateral, chronic otitis with corresponding hearing loss of the conduction type, but no perceptive defect. The height of these subjects was between 163 and 174 cm. It was stated that a sister of the proband's deceased paternal grandfather and her daughter presented a body build somewhat similar to the proband's. On examination in their home, their heights and weights were found to be 170 cm and 75 kg and 176 cm and 82 kg respectively. The length of their right middle fingers and the soles of their feet was 11 cm/26 cm and 10.5 cm/27 cm respectively, i.e. normal measurements. However, both showed slightly acromegalic features.

Thus, no further cases of Marfan's syndrome or components thereof were found in the pedigree.

Discussion

The disease is congenital, but it is usually not detected until the period of maximum longitudinal growth, i.e. at the age of 12-15 (Nielsen, 1941), although

cases in younger children, even in newborns and in infants, have been reported (Schreiber *et al.*, 1928; Benedict, 1936; Chiari, 1937). This explains why it was not observed in the present case on the occasion of previous medical examinations, such as the first admission to the E.N.T. department, or noted by the parents until school age. It is worth bearing in mind—as also stressed by Nielsen—that the "condition is far too often detected too late because it is not sufficiently known", and is then interpreted as an ordinary lanky habitus. This is all the more regrettable as orthopaedic treatment should be instituted in time in order to prevent the frequently severely progressive kyphosis and as ophthalmological examination ought to disclose a possible dislocation of the lens in time so that protective measures—as suggested in the present case—may prevent exacerbation; the same applies to the frequently associated heart disease.

Our patient also had a right-sided chronic otitis and—apart from a consequent hearing impairment of the conduction type—an evident hearing loss of the perceptive type involving both sides, which must be presumed to be unrelated to her previous and present otitis. As a rule, only prolonged and severe cases of otitis involve the inner ear, giving rise to perceptive hearing loss in addition to the hearing loss characteristic of otitis with loss of low tones. The occurrence of otitis in the presence of Marfan's syndrome was presumably a chance coincidence, as otitis is not known to be included in any special symptom complex (apart from infectious diseases), especially not in Marfan's syndrome, although the asthenic constitution might be imagined to predispose to otitis.

Incidentally, otitis was present in another 3 members of the family which must be presumed to have a predisposition to this aural disease. On the other hand, nerve deafness (=perceptive deafness), partial or total, is occasionally included in a number of syndromes, e.g. retinitis pigmentosa, idiocy or other diseases of the central nervous system, astigmatism, dyslexia, or speech disorders (Bell, 1922; Curtius, 1933; Heinonen, 1933; Steinberg, 1937; Henry, 1947; Johnsen, 1954; Everberg, 1957). Nerve deafness was not found among the other members of the family who were examined. Among those who answered questionnaires, impaired hearing was present only in the above-mentioned cousin in whom objective examination revealed chronic otitis with some conduction deafness ("middle ear deafness"), but no perceptive loss ("nerve deafness"). To be absolutely certain that no further cases of partial nerve deafness were present in the family, one would have to examine all its members, as mild and moderately pronounced cases—such as the proband's—are best disclosed by audiometry.

If the proband presents a solitary case of perceptive hearing loss, the question arises whether this defect is related to Marfan's syndrome. Perusing the literature on Marfan's syndrome with a special view to hardness of hearing or deafness, the author found that this was mentioned by Ganther (1927), Brock (1929), and Schilling (1936). All these cases, however, were somewhat atypical. In the first-mentioned case the hearing loss was of the conduction type, whereas in the other two it was of the perceptive type. Bücklers (1935) has reported a case of arachnodactyly, ectopia

lentis, and "Innenohrschwerhörigkeit" in an 8-year-old boy who was, moreover, somewhat mentally retarded. Lloyd (1937) mentioned two cases of typical Marfan's syndrome with arachnodactyly and ectopia lentis in a pair of siblings who had also been deaf from birth.

It cannot be said with certainty whether these 5 cases of perceptive deafness, occurring among approximately 350 cases of Marfan's syndrome, exceed what might be expected statistically. The incidence of partial nerve deafness in children is 2 in a thousand (Johnsen, 1954), whereas the incidence of deaf-mutism is $\frac{1}{2}$ in a thousand (Lidenov, 1945; Kemp, 1951). No doubt, the figures are too small to evaluate the occurrence of a hearing defect in Marfan's syndrome. As evident from McKusick's "Pedigree of Causes" (1956), which includes also deafness, and from the introduction, the concept of Marfan's syndrome has been perceptibly extended during the 60 years that it has been known. Possibly, chance findings are incorrectly assigned to this polymorphous syndrome. Perhaps this also applies to the hearing defect in the present case. On the basis of the literature, however, it seems justified to report the present case in order to call the attention of pediatricians to the possibility of inner ear involvement (on a connective-tissue basis?). The best approach to this question would seem to be audiometric study of all patients with Marfan's syndrome. It must be borne in mind that most cases of moderate hearing loss of the perceptive type are not directly recognized, as the hearing of spoken voice is normal.

Summary

A girl of eleven years with typical Marfan's syndrome exhibited in addition a high-tone hearing-loss.

From the literature it seems that perceptive deafness among patients with Marfan's syndrome possibly occurs more frequently than might be expected statistically. It is recommended that audiometric study be done in all patients with Marfan's syndrome.

Syndrome de Marfan compliqué de surdité partielle. Observations relatives a un cas survenu chez une petite fille appartenant à une paire de jumeles.

Une petite fille d'onze ans atteinte d'un syndrome de Marfan caractéristique présentait en outre une abolition de l'acuité auditive à l'égard des sons aigus.

D'après la littérature, il semble qu'une diminution de l'acuité auditive à l'égard de certains sons pourrait bien être plus fréquente chez les sujets atteints de syndrome de Marfan que ne l'indiquent les statistiques. L'auteur recommande de procéder à des examens audiométriques chez tous les malades atteints de syndrome de Marfan.

Das Syndrom von Marfan vergesellschaftet mit Hörverlust. Mitteilung über einen Fall bei einem Zwilling.

Ein elfjähriges Mädchen mit einem typischen Syndrom von Marfan wies überdies einen Gehörverlust für hohe Töne auf.

Aus dem Schrifttum scheint hervorzugehen, dass perzeptive Taubheit bei Kranken mit dem Marfanschen Syndrom möglicherweise häufiger ist, als es die Statistiken erwarten lassen würden. Es wird der Vorschlag gemacht, alle Kranken mit dem Syndrom von Marfan audiometrisch zu untersuchen.

Síndrome de Marfan asociado con un defecto de la audición. Presentación de un caso en uno de dos gemelos.

Una muchacha de once años con un síndrome de Marfan presentaba además una sordera para los tonos agudos.

Se desespera de la literatura que la sordera de percepción aparece en enfermos afectos de un síndrome de Marfan con mayor frecuencia de la que cabría esperar según la estadística. Se recomienda el estudio audiométrico de todos los pacientes afectos de un síndrome de Marfan.

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Ingemannsvej 24
Copenhagen V
Denmark

CASE REPORT

Infantile Agranulocytosis of Probably Congenital Origin

by FOLKE HEDENBERG

From the Children's Hospital, Hålsingborg, Sweden. (Head: Nils Lindquist, M.D.)

Agranulocytotic conditions in children are very different regarding the pathogenesis.

In 1956 Kostmann described a newly discovered disease; Infantile genetic agranulocytosis, and was of the opinion, that the disease is probably caused by a primary insufficiency of the bone marrow leading to a maturation arrest in myelopoiesis. He presented fourteen children of both sexes belonging to nine families. In six cases there were more detailed clinical and histological studies. Three children had more or less pronounced agranulocytosis and died of severe infection before the age of six months. One child lived until the age of three years, with a constant agranulocytosis, discovered at the age of ten months, but with infections starting already at 2½ months of age. The bone marrow showed a maturation arrest at the myelocytic stage. Cell culture experiments with the patient's bone marrow in his own serum revealed a maturation and activation of the cells, when cysteine was added. Therefore, cysteine was given to the patient in various manners, but with no result. Two children had milder forms of the disease and were still alive at the age of four years. The remaining eight children were not clinically studied, but all of them had died before the age of two months in septic conditions with skin abscesses. Genetic analysis was per-

formed and the disease was considered to be caused by a single recessive autosomal gene difference.

The purpose of this paper is to present a case of agranulocytosis, probably of congenital origin, discovered as early as at the age of one week. There is a good agreement with infantile genetic agranulocytosis.

Case report

E.L.J., a girl, was born on March 13, 1957. Birth weight 2950 g. Normal delivery after an uncomplicated pregnancy. Both mother and child belonged to blood group 0 Rh +. BCG-vaccinated. She was the sixth child of healthy parents. Her siblings were born in years 1935-1949 and all of them had been healthy and they had never had any severe infections or skin abscesses.

The first days of observation the girl was in a good condition, sucked well from the breast, and after the initial weight fall she gained weight fairly well. On March 19 she got fever, which continued the next day. She was admitted to the Children's Hospital of Hålsingborg on March 20. On admission her general condition was unimpaired, the pharynx was a little reddened and the tympanic membranes were not quite pale. The superficial lymph nodes, liver and spleen

were not palpable. Physically the heart and lungs were normal. Lumbar puncture was performed with normal spinal fluid findings. Despite treatment with penicillin an otitis media developed and paracentesis was done on March 26.

Blood examinations revealed a constant granulocytopenia and a bone marrow examination gave a pathological pattern. The following months the girl had relapsing otitis media and a conjunctival infection. At the age of six weeks she developed convulsions and her general condition was affected. Lumbar puncture was done again, but the spinal fluid was clear, the protein reactions and the cells normal. After a week she had improved and on May 23 she was discharged in good health but with a remaining pronounced granulocytopenia.

When four months old the girl was readmitted with high fever, infections of the fingers, furuncles of the right thigh, the gluteal regions and the neck. The granulocytopenia remained. The skin processes

healed with antibiotics and the girl was discharged in good condition. One week later she was readmitted with fever and otitis media and from then she remained in this hospital until the age of ten months. During this period she had relapsing otitis media and a furuncle near the anus. The last month before discharge she was free from infections regardless of a hordeolum and conjunctival inflammation. Being discharged on January 8, 1958, she was admitted again after a week with a furuncle in the right auditory canal. With antibiotics her condition improved. The girl moved from this town and has not been seen here after that. However, she was hospitalized at the Pediatric Department in Kristianstad from January 24 until her death on April 28, 1958. She had a suppurative otitis media and was treated with various broad-spectrum antibiotics, penicillin and Lederkyn. The effect was not so good. During the last weeks of her life she had repeated cutaneous abscesses, convulsions of grand mal character and fever. She

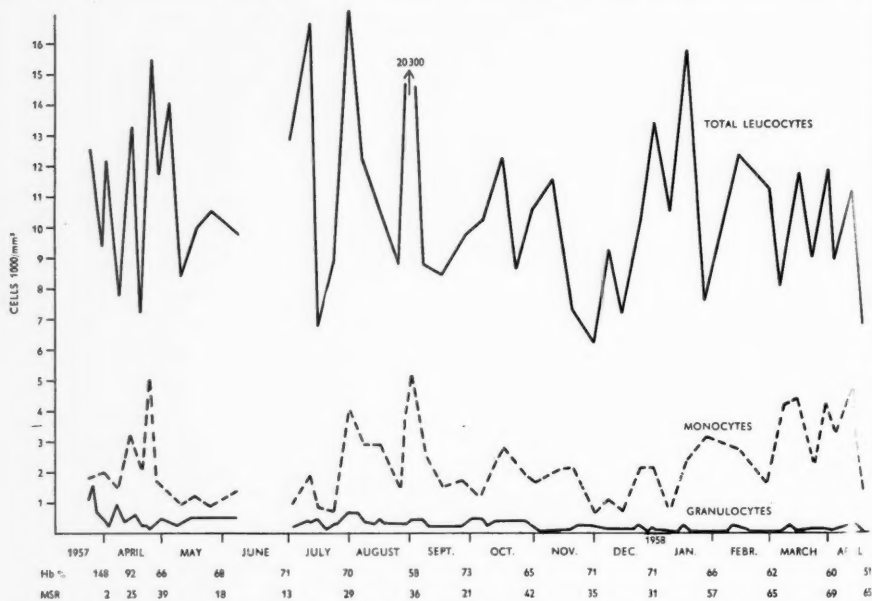


Fig. 1. The blood values graphically reproduced. The micro-sedimentation rate has been estimated a.m. Landau in Hälsingborg and a.m. Ström in Kristianstad.

also vomited very much and ante mortem her weight was 6600 g.

The blood examinations have been illustrated in Fig. 1. The number of platelets per cubic millimeter varied between 190,000 and 392,000, and the reticulocytes between 2 and 5 promille. Normal prothrombin time. Non protein nitrogen was normal. The urine did not contain protein, sugar or pathological elements. The total serum protein level was normal and the electrophoretic pattern normal. Examination of the blood for leucocyte agglutinins gave negative results in two investigations. Paul-Bunnells reaction was negative. The total urinary excretion of amino acids was normal and so was the excretion of the individual amino acids.

Bacteriological cultures from abscesses in July 1957 gave no growth. Cultures of feces were negative. Discharge from the ears in February and March 1958 gave growth of *Pseudomonas pyocyaneus*.

X-ray examinations of skull, heart and lungs showed no abnormalities. EEG-examination was normal. Ophthalmoscopy revealed nothing abnormal. Tuberculin reaction was positive after BCG-vaccination.

Repeated *bone marrow examinations* have been performed. The first preparation in March 1957 showed an atypical structure and there was dominance of lymphocytic elements, only 0.5 per cent polymorph-nuclear leucocytes. There was maturation arrest at the myelocytic stage. This block in myelopoiesis was then the main characteristic in all bone marrow preparations and the cells often appeared atypical. After subcutaneous injections of cysteine there was slight increase of granulocytic immature forms but no mature leucocytes. Corticosteroids, folic acid, vitamin B₆ and vitamin B₁₂ had no influence upon the bone marrow picture.

Post-mortem examination

External appearance: Highly emaciated girl. Cutaneous abscesses scattered over the body.

Gross findings: The brain and meninges showed no changes. The heart was normal.

The pleura did not contain any fluid. The lower lobe of the right lung was essentially consolidated. The liver and spleen were of normal size and consistency. The kidneys and adrenals were normal. The mesentery contained abundant firm lymph nodes with the size of peas and beans.

Microscopic appearance: The lung showed an unspecific bronchitis with multiple areas of atelectasis and multiple pneumonic areas. The bone marrow was relatively poor in cells and showed a rather rich accumulation of fat. There were numerous erythropoietic elements. In the myelopoiesis the mature leucocytes were very few in number. In the bone marrow no lymphocytes could be seen. The lymph nodes showed no remarkable changes.

Special investigations

Cell culture experiments with bone marrow were performed by Dr. Phil. C. Munk Plum, Dianalund, Denmark.

The bone marrow preparation was relatively rich in cells. Principally myelopoiesis seemed to be inhibited after the promyelocytic stage. In the cells of leucopoiesis there were some mitoses, but several of them were atypical, often with more or less divisions in the same cell. All the mature leucocytes, few in number, had a stab nucleus, which was short and plump, and the structure was rather loose. The megakaryocytes were very few but of normal structure. The reticulum cells were large and rather irregular considering both nucleus and protoplasm. The lymphocytes were of a very irregular size. There were a predominating number of small cells with pyknotic nucleus. The cells of erythropoiesis showed a distinct shift to the left, no megaloblasts but numerous macroblasts. There was a pronounced anisocytosis.

(1) Culture of the patient's bone marrow in her own serum.

The culture experiments were performed at 37°C and determinations were done at 0, 3, 6, 9 and 24 hours. The regeneration of erythrocytes calculated per normoblast per hour was determined. The regeneration on an

average, by these determinations was 4.00, which is lower than the normal of 5.39, i.e. 74% of the normal bone marrow activity.

(2) Culture of the patient's bone marrow in the serum of a normal child.

There was a bone marrow activity of 4.70 with one normal serum and 4.82 with another, that is a better activity than in the patient's own serum. Normally myelopoiesis will not show any changes during the time of the experiment. In this patient, however, there was a tendency to normal development. After 6 hours a slight increase of stab nucleated, mainly metamyelocytes, could be seen and after 24 hours an increase of stab nucleated granulocytes was found.

(3) Culture of normal bone marrow in the patient's serum.

Normally a reduction of bone marrow activity with about 15 per cent is observed when culturing normal bone marrow in normal serum. In this case a greater reduction was found, namely 32 per cent, suggesting that the patient's serum lacked substances necessary to maintain a normal bone marrow activity. On the other hand, the serum could possibly contain unknown inhibitory substances.

(4) Culture of the patient's bone marrow in her own serum with addition of 1 promille tyrosine.

This experiment gave the same result as experiment (1).

(5) Culture of the patient's bone marrow in her own serum with added cysteine.

The cysteine was added in amounts equivalent to 0.3 mg per 100 ml serum. In this experiment a slight increase of erythropoiesis was found, the value was 4.75. Without added cysteine the regeneration was 4.00 and then a good effect of cysteine could be obtained. There were also changes of myelopoiesis as in experiment (2). The differentiation, however, was observed after 9 hours incubation.

(6) Culture of the patient's bone marrow in her own serum with added liver extract.

The results were the same as in experiment (1).

(7) Culture of the patient's bone marrow in her own serum with added vitamin B₆.

Vitamin B₆ was added in amounts equivalent to 0.01 mg per 100 ml serum. The results corresponded to those under (5).

Conclusion: In culturing the patient's bone marrow a decreased bone marrow activity was observed using the patient's own serum as a substrate. An increased activity was seen when using normal serum. Addition of cysteine and vitamin B₆ had a favourable effect upon the bone marrow activity. An activation of cell differentiation thus followed addition of sulphur-containing amino acids.

Discussion

Concerning the differential diagnosis the thought at first fell upon transitory granulocytopenia in new-born (Lehndorff 1951; Luhby & Slobody 1956). This condition is characterized by a pronounced granulocytopenia and a maturation arrest in the bone marrow with a duration of up to four weeks.

Chronic granulocytopenia in children has been described by several authors. A characteristic feature is the pronounced granulocytopenia of varying duration and a tendency to infections. Normal bone marrow and spontaneous cure is described by Salomonsen 1948 and Ström 1949. They also point out that the disease starts after the age of six months. On the other side bone marrow changes and an earlier onset of the disease have been described (Hotz 1941; Tobler 1942; Vahlquist & Anjou 1952). Of these cases several had a spontaneous cure after varying duration. Two cases (Hotz 1941 and Tobler 1942) are similar as to those presented by Köstmann as to the actual case.

Granulocytopenia caused by various drugs, radiation, toxic damage and

plastic infiltration of the bone marrow can be eliminated in the present case. The child was only breast fed and had not received any drugs. During the pregnancy the mother had been given drugs not known to cause granulocytopenia. She had not been X-rayed.

Cyclic agranulocytosis is described amongst others by Vahlquist (1946) and is not relevant to this case, as the disease has not run a periodic course.

The disease in this patient is most likely analogous to that described by Kostmann (1956). There are a great many similarities: the age of onset, the clinical signs and course, the pronounced agranulocytosis, the bone marrow changes, the concurrent monocytosis. However, no hereditary and genetic factors have been found. Blood counts of her family were normal. All of them had been healthy as children. The mother had ten brothers and sisters. One sister died in pneumonia at the age of 1 year and it is not known if she had skin infections or abnormal blood count. Both parents were born in Skåne and so were their parents. No consanguinity is known and there is not any known relation to the families in the North of Sweden described by Kostmann.

The monocytosis is of special interest. In this case a varying connection with the infections and monocytosis could be observed. In the case described by McLean the monocyte count varied from 4 up to 53 per cent, but there was no relation between the monocyte count and infections (personal communication). Tobler & Busser-Plüss (1942) found that the monocytes have a compensatory phagocytic function in patients suffering from agranulocytosis. Therefore, the increased num-

ber of monocytes in this case possibly reflects a compensatory phagocytic effect.

Erythropoiesis was very little affected. The anemia observed during the first months was probably secondary to infections. Blood transfusions have corrected the lowered hemoglobin and red blood cells but have not had any effect on the leucocytes. In the last bone marrow smear (March 1958) there were signs of exhaustion of erythropoiesis.

The cell culture experiments revealed an increasing maturation and differentiation of the cells of myelopoiesis, when cysteine and vitamin B₆ were added to the medium, or when normal serum was used. A therapeutic trial with vitamin B₆ perorally had no effect. Concerning the cysteine it is known that sulphur-containing amino acids play an important role in the leucocyte metabolism. In normal bone marrow a high sulphhydryl content has been observed in myeloblasts and there is a decreasing amount during the differentiation and maturation (Munk Plum 1951). If bone marrow is cultured on synthetic medium with lack of cysteine a rapid cell degeneration develops. Cysteine added to the medium exerts a protecting influence especially on the granulocytes (Baldini & Sacchetti 1950). It is well known that nitrogen mustard therapy gives a leukopenia including granulocytopenia, but cysteine counteracts this (Weisberger & Heinle 1950). Closely related to cysteine is glutathione and this substance is supposed to have a stimulating effect on the cell division (Parker & Kracke 1936). In a patient suffering from granulocytopenia Contopoulos & Andersson (1950) found a lower glutathione level than normally.

In the present case there is probably a congenital defect of the patient's ability to utilize the sulphur-containing amino acids. Possibly the myeloblasts do not contain enough sulphhydryl groups, and therefore

maturation and differentiation can reach no longer than to the myelocytic stage. Kostmann suggests that a primary insufficiency of the bone marrow is the cause of the disease, but, as no blood counts or bone marrow smears have been made in his cases immediately after birth or during the first week this has not been proved. This case, however, would support the theory, that the disease is congenital. A pronounced granulocytopenia was discovered already on the eight day of life.

Since it is possible that sulphur-containing amino acids can be of value therapeutically, a trial was done with cystine perorally and cysteine subcutaneously but without obvious effect. Nor did therapeutic attempts with cortisone, vitamin B₁₂ and folacine have any effect. To ascertain whether ACTH could be of value, the effect of intramuscular injection of 10 I.U. of ACTH was studied in the same manner as was done by Stahlie (1956). In his case the polymorphnuclears rose from 7 to 27 per cent after 2 hours but again decreased to 8 per cent after 6 hours. In the present case there was no effect of ACTH (Fig. 2). Therefore, no treatment with ACTH was given. The recurrent infections has been

counteracted with antibiotics and chemotherapeutics. The girl has also been given some intramuscular injections of gammaglobulin in order to increase the resistance against infections.

When the girl was 13½ months old the disease lead to death and it was obvious that the resistance against infections was extremely low. The course and the changes from time to time in the bone marrow smears are very similar to those in Case R 4 (Kostmann, personal communication). There was also a good agreement with the cell culture experiments, which were performed by the same investigator.

Recently further cases of probably congenital agranulocytosis have been published. McLean (1957) reported a case of chronic neutropenia in a girl of 23 months, who had recurrent infections since birth. The peripheral blood showed a fluctuating granulocytopenia during her stay at the hospital. The bone marrow showed an inhibition of myelopoiesis at the myelocytic stage. Various therapeutic measures were taken but with no result. No hereditary factors could be found. A complete neutrophilic agranulocytosis remained, when the girl was 4 years 3 months old in March 1957. She had been constantly treated with antibiotics after discharge in July 1955.

Luhby *et al.* (1957) described a case of agranulocytosis, in their opinion of congenital character. A 3½ month old boy had repeated infections since the age of two weeks, and the agranulocytosis was discovered, when he was six weeks. He died at the age of seven months in a staphylococcal pneumonia with multiple abscess formations. Blood counts showed between 4100 and 24,300 white cells per cubic millimeter with almost complete absence of neutrophils during the observation time. Bone marrow examinations revealed a striking reduction of neutrophilic myeloid cells.

Kniker & Panos (1957) presented two in-

ACTH 10 I.U.	WBC	Metamyelo- cytes	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
Before inj.	7600	—	—	—	1	91	8
After 1 hour		1	1	—	1	90	7
After 2 hours		—	—	—	—	89	11
After 4 hours		—	—	—	1	89	10
After 8 hours		1	—	—	—	86	13
After 24 hours	8400	—	—	1	2	85	12

Fig. 2. The influence on the differential count after intramuscular injection of 10 I.U. ACTH.

infants, seven and thirty months of age, with pronounced skin and respiratory infections since early infancy. In the bone marrow there was a consistent pattern of hypercellularity and maturation arrest at the myelocytic stage and further a plasmocytosis. A hypergammaglobulinemia was found in both. One patient died suddenly in a probably meningitis and the other died with overwhelming sepsis. Both children had constant severe neutropenia during their stay at the hospital.

Larsen (1957) related a case of extreme neutropenia in a boy, 9½ month old, who had complete absence of neutrophils in the peripheral blood and in the bone marrow. Since birth there had been furunculosis. The disease could not be influenced by corti-

costeroids. It was supposed that the underlying cause was a defect in the bone marrow.

There is a good accordance with the related cases of agranulocytosis concerning the appearance of the illness, the recurrent infections, the bone marrow picture and the peripheral blood count. The clinical course and the blood changes, however, can be very similar, but the etiology of an agranulocytotic condition, nevertheless, is heterogeneous. Concerning the cell culture experiments and the role of cysteine in the pathogenesis no definite conclusions can be drawn.

Summary

A case of probably congenital agranulocytosis is reported. A girl was found to have a pronounced granulocytopenia a week after birth in connection with an infection. The condition was then constant and a total agranulocytosis developed and she had recurrent infections, which lead to death at the age of 13½ months. In the bone marrow a constant maturation arrest at the promyelocyte-myelocyte stage was observed. Culture experiments with the patient's bone marrow revealed a maturation and differentiation of the cells of myelopoiesis when sulphur-containing amino acids were added. Cysteine therapy had no certain effect. A primary insufficiency of the bone marrow is suggested to be the cause of the disease.

Agranulocytose infantile, probablement d'origine congénitale.

Le cas d'une agranulocytose congénitale possible est rapporté. On a trouvé chez une fille une granulocytopénie prononcée une semaine après la naissance en rapport avec une infection. L'état était alors inchangé et une agranulocytose totale se développa. Elle eut des infections récurrentes, qui entraînent la mort à l'âge de 13½ mois. On a observé dans la moelle épinière un arrêt constant de la maturation au stade promyélocyte-myélocyte. Des expériences avec culture de la moelle épinière de la malade démontrèrent une maturation et une différenciation des cellules myélopoïétiques lorsque l'on ajoute des acides aminés contenant du soufre. Un traitement par la cystéine n'a eu aucun effet sûr. Une insuffisance primaire de la moelle épinière est suggérée être la cause de la maladie.

Kindliche Agranulocytose wahrscheinlich kongenitalen Ursprungs.

Im Fall von wahrscheinlich angeborener Agranulocytose wird beschrieben. Bei einem Mädchen wurde festgestellt eine ausgesprochene Granulocytopenie eine Woche nach der Geburt im Zusammenhang mit einer Infektion. Der Zustand blieb damals konstant und eine totale Agranulocytose entwickelte sich. Es hatte wiederholte Infektionen, welche im Alter von 13½ Monaten zum Tode führten. Im Knochenmark wurde eine konstante Reifehemmung im Promyelocyten-Myelocyten- Stadium beobachtet. Kulturanlagen mit dem Knochenmark der Patientin enthüllten eine Reife

und eine Differenzierung der Zellen der Myelopoëse, wenn schwefelhaltige Aminosäuren hinzugefügt wurden. Cystein-Therapie hatte keinen sicheren Einfluss. Es wird angenommen, dass eine Primärsuffizienz des Knochenmarks die Ursache der Krankheit ist.

Agranulocytosis infantil de probable origen congénito.

Se describe un caso de probable agranulocytosis congénita. Se descubrió una intensa granulocitopenia en una niña una semana después del nacimiento, en relación con un proceso infeccioso. La enferma presentó infecciones recurrentes que la llevaron a la muerte a la edad de trece meses y medio. En la médula ósea se observó una detención constante de la maduración en la fase de promielocito-mielocito. Los experimentos realizados con el cultivo de la médula ósea del paciente demostraron la maduración y diferenciación de las células de la mielopoiesis al añadir aminoácidos sulfurados. La terapéutica cisteínica careció de efectos seguros. Se sugiere que la causa de la enfermedad es una insuficiencia primaria de la médula ósea.

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Banckska sjukhuset
Hälsingborg
Sweden

REVIEW ARTICLE

A Review of Cow's Milk Allergy in Infancy¹

by J. P. STANFIELD

There are few subjects in which there is such a wide tangle of views as in the problem of milk allergy. In the following pages an attempt is made to unravel the positions at the moment. The fundamental nature of allergy will not be discussed, though the vagueness of the definition of allergy as a state of sensitivity of the tissues to ordinarily nontoxic substances, based on the antigen-antibody reaction, is one of the main reasons why the subject under examination is so unclear. An important question which has therefore been omitted is the synonymy of allergy and sensitivity. Most authors appear to use these terms as if they were based on the disturbed antigen-antibody reaction, defined as "allergy". This may not be true, especially for example, in conditions of gastrointestinal sensitivity to cow's milk, which have been described as allergic in nature by many authors, but which may well be due to some very different mechanism. The subject of this paper therefore should more correctly be termed "the problem of sensitivity to cow's milk in infancy". With this in mind, however, the terms allergy and sensitivity have been used here, as in the literature, almost synonymously.

Answers to the following questions have been sought from the literature.

- (1) Can disease due to allergy to cow's milk be defined?
- (2) *a.* How common is this disease?
b. How often is allergy to cow's milk a factor of importance in the so-called allergic diseases of infancy?
- (3) What are the best methods of treatment?

It was found that most of the answers to these questions are based on subjective clinical methods and that objective experimental effort in this field is not only scarce but as yet has given no clear-cut answers.

1. Can Disease due to Allergy to Cow's Milk be Defined?

Two very different approaches to this problem need to be studied, viz. (*a*) immunological, and (*b*) clinical. Under a third heading can be considered (*c*) the correlation between these two approaches.

Immunological aspects

It has been known for a long time that cow's milk proteins are highly antigenic. As early as in 1901 Moro and, in 1902,

¹ This review has been written during a course of study at the Paediatric Clinic, Akademiska Sjukhuset, Uppsala.

Field were experimenting on the changes in these antigenic properties produced by heating.

Wells and Osborne in 1921 studied the anaphylactic properties of purified milk proteins, using the immunological specificity of each fraction to demonstrate the purity of the prepared proteins. They separated milk proteins into four groups, each distinct immunologically and chemically: these were casein, lactoglobulin, lactalbumin and an alcohol extract of casein. This work was utilised by Ratner & Gruehl in 1935 to study the changes that might have occurred in heated milk. These authors review the early work on milk immunology fairly thoroughly; their findings will be referred to later. Besides producing precipitins, complement fixing antibodies and anaphylaxis in sensitised animals, cow's milk has also been shown to produce precipitins in the blood of infants fed on cow's milk from birth. Schloss *et al.* in 1925 demonstrated this and found that the appearance of the precipitins was associated with positive skin tests for cow's milk. Both these phenomena were temporary and disappeared in a few weeks despite continued milk feeding. They tended to reappear in the presence of gastro-intestinal disorders due, the authors thought, to a temporary increase in absorption of larger protein molecules in these conditions.

György *et al.* (1931) found complement fixing antibodies to cow's milk in 40 of 69 healthy artificially fed infants, and this was confirmed by Strobl & Wasitzky (1932) in 43 of 224 specimens of serum from such cases. Lippard, Schloss & Johnson (1936) followed up the earlier work of Schloss and György. They used the complement fixation test in the detection of cow milk antigen

and antibody in the serum of 229 normal infants and adults aged from 1 day to 30 years, none of whom were suffering from gastro-intestinal disease, and all receiving a normal diet for their age. It was found that no antigens or antibodies appeared in the serum until the infants were fed cow's milk. Cow's milk protein appeared in the serum within a few days of its first being ingested, and was present in 60-90% of infants from the 4th to the 20th day. After this, measurable levels diminished rapidly in frequency of appearance; only isolated instances were observed after the 5th month, and with one exception never after the 20th month. Antibody titres appeared between the 8th and 50th day after commencing cow's milk, and were present in practically all infants between 1 and 15 months. The percentage of positive titres then fell sharply until no antibody could be detected after the fifth year. This work has been confirmed by Berger in 1953.

The direct skin test has been widely used alone or in conjunction with other immunological methods in demonstrating the development of a reaction to cow's milk proteins. This skin reaction, if positive, develops as a red wheal and flare reaching a maximum up to half an hour after either a scratch or intracutaneous inoculation of cow's milk. It persists for an hour or so and then fades within three or four hours. A delayed reaction may occur 24 to 72 hours after the test has been performed, and this is much more common with the intradermal method; there may or may not have been an immediate reaction. The significance of the delayed reaction is not known (Matheson 1954).

In 1925 Schloss *et al.* demonstrated positive skin reactions to cow's milk in the first 6 weeks of life in normal infants; these were transient in spite of continued milk feeding. On the other hand, skin s n-

sitivity can occur without any history of contact. Ratner presumed this to be a sensitivity transferred in utero. Hill (1955) in pointing out that a positive skin test might develop after some months, and yet without a history of contact with the substance, suggested that antigens transferred from the mother persist in the infant's system until the formation of a satisfactory antigen antibody reaction. In respect of this, Matheson *et al.* (1952) have shown that the skin of a newborn is capable of reacting to histamine, and of fixing passively transferred antibodies.

There is no doubt that cow's milk proteins are not only strong antigens but also enter the blood stream and produce an antibody response in a large percentage of normal infants. This fact produces considerable difficulties, as will be seen, when the correlation between clinically suspected allergy and the experimental demonstration of an antigen-antibody response is attempted.

Clinical aspects

The clinical condition of allergy to cow's milk must first be considered. This can be described, as abstracted from the literature reviewed, under four headings.

1. *Rare cases of acute anaphylactic reactions* with shock-like symptoms, occurring up to half an hour or longer after ingestion of cow's milk, usually in infants up to 1 year old. Some of these cases were reported by Hill (1939). Collins-Williams (1955), collected 29 cases in the English literature in a good review of the subject.

In the Scandinavian literature there are a few reports of allergy to cow's milk, the predominant symptom of which seems to

have been "shock". These reports are reviewed by Vendel (1948) who added 23 cases abstracted from the records of four Stockholm hospitals in a period of 28 years. Of these 23 cases 13 were described as manifesting "shock" or collapse either immediately or from 2 to 6 hours after ingestion of cow's milk. The majority also had gastro-intestinal symptoms, in the nature of diarrhoea and vomiting. The author described two types of cases, one in which an immediate allergic response occurred in an already "allergic" infant, and the second in which a delayed response occurred in an otherwise healthy infant up to 6 hours after exposure.

It is doubtful if cow's milk was responsible for the symptoms described in all of these infants. These cases are rare, but form the only well-defined condition attributable to cow's milk allergy, and merit further study.

2. "*Recognised*" allergic symptoms such as eczema, asthma, urticaria, rhinitis, which seem to be due to cow's milk and disappear when it is withdrawn from the diet, only to reappear regularly on reintroduction of the milk. (See below.)

3. *Gastro-intestinal symptoms*: a wide variety of these have been blamed on cow's milk allergy. Many workers claim that colic has often an allergic basis (Rowe, 1944; Buffum, 1951; Rosenblum, 1952; Clein, 1954; Wessel *et al.*, 1954). The coeliac syndrome and recurrent chronic diarrhoea (Kunstadter & Schultz, 1953) occasionally may be due to cow's milk allergy. Cases of pylorospasm and pyloric stenosis have been reported (Cohen & Breitbart, 1929; Balyeat & Pounders, 1933; McCarthy & Wiesman 1937). Gastro-intestinal allergy may be associated with an

eosinophilia of the stools. (Rosenblum & Rosenblum, 1952). It remains doubtful whether these cases of apparent intolerance to cow's milk all have an allergic basis.

4. *A collection of symptoms and conditions*, varying from character changes to frequent colds, including most of the minor ailments of infants, and found commonly in other conditions, have been attributed to cow's milk by various authors (Randolph, 1948; Rowe, 1944; Clein, 1954). The main criterion for this diagnosis has been the cessation of the symptoms on substituting hypo-allergenic foods and their reappearance when the milk is reintroduced.

The correlation between the clinical and immunological aspects

This has not been easy, and the temptation of most students in this field has been to ignore the latter and rely purely on the former for diagnosis. Investigations have been attempted to demonstrate abnormal immunological reactions to cow's milk in suspected or proved cases of cow's milk allergy.

There have been a few studies on the incidence of the titres of antibodies to cow's milk proteins in eczematous as compared with normal infants (György *et al.*, 1931, 1932; Strobl & Wasitzky, 1932; Zambrano & Pezza, 1935; Lippard *et al.* 1939).

György, and also Strobl & Wasitzky, reported the presence of complement fixing antibodies to milk in the blood of infants with eczema. They noted that these were measurable in much higher dilutions than in normal infants and

demonstrated the "prozone" phenomenon indicative of high titres. This finding, they thought, might be peculiar to eczema and Moro called it the "Ekzemzone".

Lippard compared the immunological reactions before and after the ingestion of eggwhite and cow's milk in a series of normal and eczematous infants. Of 24 normal infants and 5 eczematous infants never fed cow's milk, no immunological response was present. Of 46 normal infants fed cow's milk, none had positive skin tests or passive transfer tests, but 30 had positive complement fixing antibody titres, 7 of these accompanied by the "prozone" phenomenon. Of 28 eczematous infants fed cow's milk, 10 had positive skin tests, one had a positive passive transfer test, and 22 had positive complement fixing antibody titres with 21 of these showing the "prozone" phenomenon. A group of normal children between 3 and 13 years old showed no immunological response to milk protein. He concluded that these results demonstrated a quantitative difference in immunological response between the two groups. In the individual case, however, no qualitative difference could be found in the immune response which might serve to identify an abnormal antibody—antigen reaction.

In 1953, Berger found complement fixing antibodies to cow's milk in 20 of 84 children, 7 of whom were considered allergic to milk, without further clarifying the situation.

There seems to be a very indefinite correlation between the presence of antibodies in the serum and positive skin reactions. Zambrano & Pezza, (1935) for instance, in 63 cases of eczematous skin conditions found 14 with titres of complement fixing antibodies to cow's milk protein in the serum. Of these only 10 had positive skin reactions whose strength did not appear to vary with the titre of antibodies found. Eleven other cases out of the 53 had positive skin reactions without any

titre of antibody measurable in the serum. In Lippard's work in 1939, 30 normal infants were found to have complement fixing antibodies in their sera associated with negative skin reactions to the proteins involved. Though there seems, from these and other papers, to be an overall positive correlation between the antibody titre and the skin reaction, in the specific case any combination of the two may be present.

The relationship between the skin reaction and clinically suspected or proved cases of cow's milk allergy has been more extensively studied with no more success. Of recent papers, Matheson (1954) reviewing the value of skin tests in allergy reported 4 positive scratch tests and a further 6 positive intradermal tests to milk in 37 infants with atopic dermatitis. In 1955, Hill stated that he had found 17 positive scratch tests to milk proteins in 153 eczematous infants, presumably consecutive cases. Out of 100 eczematous babies under 1 year who gave positive skin scratch tests to something, 26 were positive to cow's milk. Ratner in 1956 demonstrated a frequency of 28 % positive skin tests to cow's milk in a series of 64 infants suffering from major allergic disorders (asthma, eczema, hay fever or urticaria). Of the 18 who showed a reaction, there was no case of reaction to milk alone. Unfortunately in these series there was no record of the relation between the positive skin reaction and the response to a cow milk free diet.

Collins-Williams (1955) reviewed the literature on acute anaphylaxis to cow's milk and showed that there was no correlation between this condition and the presence of a positive skin test to milk.

In Bachman & Dees (1957) series of 109 cases of allergy in babies under 2 years old, 24 out of 33 suspected on clinical grounds of having cow's milk allergy gave positive skin tests to the milk, whereas out of the 76 in which milk allergy was not suspected there were only 13 positive reactors.

Two factors which appear to affect the number of positive skin reactors in this condition are firstly the method of administering the skin test dose, and secondly the substances used as antigens. On the whole the intracutaneous injection of the antigen gives considerably more positive results than the application of the antigen to a skin scratch. Which test should be regarded as giving a truer estimate of clinical sensitivity is not known, but Hill regards a positive scratch tests as more valuable in this respect. As regards the second point it seems that purified individual milk proteins give fewer positive skin reactions than whole milk (Loveless, 1950). Most of the positive reactions are given by the lactalbumin fraction, 14 out of 18 cases in Ratner's series (1956). Ratner believes that estimation of the skin sensitivity to individual milk proteins is important in the rational therapy of the allergic condition, for the allergenic properties of lactalbumin can be largely eliminated from the milk by boiling or evaporating it (see below).

It would seem in general that positive skin tests signify past or present, active or potential sensitivity of the skin to the substance producing them. They are valuable in allergic conditions only in so far as they may indicate the allergens involved. Cow's milk is never found to be the only substance producing positive skin reactions in these cases. Negative skin tests do not necessarily signify absence of sensitivity of other organs to the substance used. In addition to an individual's sen-

sitivity to a substance, there must also be an "organ sensitivity" (Hill calls this factor *X* in the skin) and an "allergic constitution", before allergic symptoms occur. Skin tests are thus of no value in the diagnosis of individual cases, though they tend to confirm this.

A condition of cow's milk allergy or sensitivity has thus far only been defined in an acute clinical form and as such is very uncommon. In other conditions, enumerated above, in which cow's milk allergy or sensitivity appears to play a part, the degree and mechanism of this has yet to be defined.

2 (a) How Common is Cow's Milk Allergy?

The answer to this varies considerably, from rare to frequent, and in studied series from 0.3% (Collins-William, 1956) to 7% and over (Randolph, 1948; Clein, 1954). The variety seems to depend on two main factors, outlined by Bachman & Dees (1957).

The first of these is the varied criteria used for diagnosis. Almost all the authors state that the diagnosis depends on the cessation of specific symptoms on elimination of cow's milk and its products from the diet and their return in identical manner on reintroducing the food on one or more occasions. The objectivity of the authors in assessing these remissions and relapses, and the manner of reporting them varies. Many rely largely on the mother's word and in fact make this their most important observation—i.e. Clein (1954) with an incidence of 7%. However, reliable the statements are, this does not seem to eliminate the unmeasurable factor

of the mother's confidence in the allergist doctor, her consciousness of allergy and the allergist's enthusiasm for having found the culprit.

Loveless (1950) realised the need for more objective clinical tests for allergy and described a "masked ingestion test" made on eight subjects who were reputedly milk allergic. She found two were definitely sensitive to milk and produced repeatable symptoms only with cow's milk; two were doubtfully sensitive with delayed symptoms difficult to assess, and four were not sensitive. She formed the opinion that sensitivity to cow's milk was uncommon, far less common than was generally supposed. Vendel (1948), as has already been mentioned, found only 23 cases of recognised cow's milk allergy over a period of 28 years in four Stockholm hospitals. He suggested that the incidence may be higher than this in Sweden, and that many mild cases were missed. Collins-Williams (1956) reviewed the literature on incidence of cow's milk allergy. He applied the clinical criteria as rigidly as possible and recorded carefully the clinical histories of the cases he discovered, which so many reviews omit to do. He excluded all cases of known allergy, and those patients in whom the mother's initial complaint was allergy, and reported an incidence of 0.3% of a general paediatric population. Of the nine cases out of 3000 seen, five seem certain, the other four are less certain on the histories he recorded.

Bachman & Dees (1957) attempted to overcome the bias by excluding cases of known allergy, by avoiding the term allergy in their interviews and by repeatedly exposing suspected cases to cow's milk over a considerable period and producing

the same reactions each time. In this way they reached an incidence of 1% of 403, healthy, full term, consecutively born babies.

As regards the presence of a positive skin test as a criterion for diagnosis, no authors depend upon this in the absence of symptoms, though many diagnose the condition when a positive skin test is associated with either major allergic disorders or the minor disturbances already referred to. Many paediatricians have discarded the skin test as of any diagnostic value. Loveless (1950) reported an incidence of 2.3% in the combined New York practices of 142 physicians, mostly allergists, who included all allergic cases with a positive skin test to cow's milk. When she added to this the incidence reported by 49 physicians who used the clinical method alone in diagnosis, the total incidence fell to 1.5%.

The second influence on the incidence of cow's milk allergy in the literature is the population of allergic cases in the series reviewed. This is always greater in those studied by allergists, and the number is not mentioned by many of these. The figures for incidence in general paediatric practice in which cases of known allergy are excluded are usually below 1% and must be distinguished from those in a weighted practice where figures up to 7% are reported. This introduces the further question now to be discussed.

2 (i) How Often is Allergy to Cow's Milk a Factor of Importance in So-called Allergic Conditions in Infancy?

The therapeutic test and subsequent provocative tests have been used by all

workers in assessing the importance of cow's milk allergy in not only well recognised allergic disorders, but in every other minor infantile upset (Randolph, 1948; Clein, 1954). The reports vary directly, it seems, with the enthusiasm of the worker for allergy.

Collins-Williams (1956) in a thorough review of the literature, quotes Davidson (1942) as stating that cow's milk produced symptoms in 40% of 100 children over 6 years of age with allergic conditions and in 55% of 20 allergic children below 4 years of age; and Rowe (1944) as finding cow's milk allergy in 20-30% of all food sensitive individuals. In an enthusiastic report, Clein in 1954 found large numbers of babies with varied symptoms, only one or two of which are usually recognised as allergic, who responded dramatically to the cessation of all cow's milk derivatives. These symptoms included diarrhoea, the coeliac syndrome, character changes, colds, constipation, anorexia, pylorospasm and colic. As regards the last symptom, Clein found this in 31% of his cases, though he does not state in how many of these it was the only symptom. Collins-Williams (1956) in 3000 cases of infantile colic found no case which he could attribute to milk allergy with certainty. He had observed cases of major allergy (eczema, asthma etc.) in whom colic was present and disappeared on withdrawal of milk, and a few referred cases in whom severe colic seemed to be the only evidence of cow's milk allergy. Reviewing the literature he quoted incidences of cow's milk allergy in infantile colic from "common" (Rowe, 1944; Buffum, 1951; Martin, 1954) to a figure of 12% (Wessel *et al.*, 1954). Rosenblum & Rosenblum (1952) reported 60 cases of gastro-intestinal disturbances (colic, vomiting and diarrhoea, singly or in combination), in which 46 cleared on changing the cow's milk either to evaporated milk or to substitute milks.

Kunstadter & Schultz (1953) found that withdrawal of cow's milk produced complete

relief in 19 out of 36 infants with chronic recurrent diarrhoea, 17 of whom began their symptoms in the first 3 months of life. Eleven of these cases, they said, resembled the coeliac syndrome and in 8 of the eleven the symptoms ceased on stopping cow's milk. In a recent report Bachman & Dees (1957) gave an incidence of 30% with milk allergy diagnosed clinically, in a group of 109 allergic babies under 2 years of age.

Thus the incidence and importance of cow's milk allergy in allergic conditions is still not known. It would be valuable to hear of some British or Scandinavian figures in this field. Edgren in his study on infantile eczema in 1942 found no difference in the number of breast fed and bottle fed infants in 395 cases. He also found that the time of onset of the eczema was not affected by the type of feeding. This is in contrast to some workers, such as Grulee and Sanford in 1936, who stated that the incidence of eczema was seven times higher in artificially fed than in breast fed infants. Two of the most experienced allergists in America conclude differently. Hill (1955) admitted that he was not so convinced that cow's milk allergy was as important a factor in infantile eczema as he had previously thought. Glaser (1956) believed that it was of great importance in all allergic conditions in babies and this was confirmed by the results of clinical trials to be mentioned below.

The impression obtained from this review of the literature is that cow's milk plays a small part in allergic conditions. It has achieved importance mainly because it is the food which most babies, allergic or otherwise, first receive after being weaned from the breast, and consume in the greatest quantity. It is rarely the only allergen responsible for the

symptoms. The most important factor is the underlying allergic constitution which will react to a variety of substances.

3. What Are the Best Methods of Treatment in Conditions where Allergy to Cow's Milk May Be a Factor?

There is no doubt that in the rare cases of acute anaphylaxis to cow's milk complete abstinence is essential (goat's milk is reported as a good substitute), and must be followed by a course of desensitisation which most workers accomplish by gradually increasing oral dosage.

In a summary of the treatment of eczema, Hill (1955) wrote from a vast experience. If a scratch test for milk proteins was positive (the incidence of this was low) then the milk should be withheld. If the baby was only sensitive to lactalbumin, as happened most frequently, then it was sufficient to give evaporated milk; goat's milk had not been very successful in eczema. In the few cases sensitive also to casein then all cow's milk derivatives should be stopped. If this produced no improvement within two weeks then there was no point in continuing to withhold the milk any longer. He gave a scheme for recommencing milk gradually after six months or so in cases who have responded. This represents a very moderate view compared to the wholesale withholding of cow's milk derivatives which has been done by other workers in all sorts of allergic or pseudo-allergic conditions with varying claims for success.

Glaser & Johstone (1953) pointed out that Grulee & Sanford in 1936 had observed that many more infants developed eczema on cow's milk as compared with

infants on breast milk. On the basis of this, Glaser and Johnstone commenced feeding "potentially allergic" infants (that is with siblings or parents with allergic conditions) on milkfree diets from birth. (These only included those who could not be breast fed.) The milk free diet consisted of a soy bean preparation, Mull Soy. They claimed that only 15 % of the babies were not able to tolerate this owing to diarrhoea and vomiting, a fact of which Hill (1955) was critical. They stated that on this diet only 8 % of 88 cases developed eczema compared with 30 % of a control group (the siblings of the experimental babies). Further, even after the experimental group had commenced cow's milk, in a follow-up which in some cases was up to 10 years, only 15 % of the experimental group developed major allergic disorders in contrast to 64.6 % of the control group. A further control group was selected from their files and chosen to resemble, as far as possible, the family history background, sex and age of the experimental group; in 175 of these, 52 % developed major allergic disorders.

The authors claimed that these results not only proved the familial tendencies of these disorders but demonstrated that they could be largely prevented by completely withholding cow's milk or its derivatives from birth to about 6 months. This important conclusion did not seem to produce much comment, and this may have been due to the withering effect of the criticism of the work by Lowell & Schiller (1954). Their comments, dismissed as minor by Glaser & Johnstone (1954), criticised the work mainly on account of the method of selection of cases for both experimental and control groups, most of

which was done retrospectively and therefore with unavoidable bias. Furthermore, they said, any selected group of cases from the files of an allergist's practice would have a higher incidence of allergy, many cases actually being brought to the authors' attention precisely because they had allergy. It is difficult to see why Glaser & Johnstone could not have used every alternate "potentially allergic" child for the experimental group, and it seems likely that they did not because the whole study was retrospective in nature. Lowell & Schiller's criticisms were reasonable and the reply of Glaser & Johnstone (1954) gave no satisfactory answer. No more work, however, has been done with more carefully controlled groups as yet, which seems strange in view of the admission by Lowell and Schiller that the conclusions from this study, if proved correct, would be of great importance in the prevention of eczema and other allergies. Hill (1955) criticised the work mainly on the danger of using soy bean preparations on account of the diarrhoea they produced.

This introduces the subject of *substitute milk preparations* which have been used in the diagnosis and treatment of conditions suspected of being due to cow's milk allergy. Presuming that human milk is unavailable, there are several substitute preparations in use. These preparations can be divided into (1) those derived from cow's milk, (2) milks from other species, and (3) substitute "hypo-allergenic" milks.

1. *Substitute preparations derived from cow's milk.*—In 1935 Ratner & Gruehl used purified cow's milk protein and the anaphylactic reaction to investigate the changes in the antigenic properties of various modifications of cow's milk. They reviewed the work

of Cutler (1929) and Lewis & Hayden (1932). These workers had used the precipitin test and the complement fixation test respectively in examining the changes in the antigenic properties of milk proteins on heating. Though their preparations were probably not very pure they showed that there was a definite decrease in antigenicity in the whey proteins (lactalbumin) when heated to over 60°C, and this became more marked as the temperature increased. Lewis & Hayden also demonstrated that no change occurred in the casein until the temperature exceeded 110°C, when there was a marked decrease in antigenic activity. Ratner & Gruehl found that evaporated milk, obtained by removing 50% of the water from cow's milk and then sterilising for 20 minutes at 116°C, and cow's milk, boiled for 4 hours, showed a definite diminution in antigenic properties of the lactalbumin fraction. In these two modifications of cow's milk, the lactalbumin fraction lost its power to produce anaphylactic shock when injected into an animal previously sensitised to lactalbumin, though it was still capable of sensitising the animal to lactalbumin. The casein fraction remained unchanged. Furthermore when these two preparations were fed by mouth there was a 50% reduction in the number of animals sensitised to whole milk, the remaining sensitisation being due to the casein fraction. This sensitising ability was reduced still further in evaporated milk by acidification, though this did not occur with ordinary cow's milk. In cow's milk modifications in which the milk had not been exposed to high temperatures, such as dried milk, pasteurised milk or acidified milk, there was no reduction in anaphylactogenic properties. The authors concluded that the loss of antigenicity of lactalbumin produced by heat was probably due to a physical coagulation, which also would delay the passage of the protein through the gastro-intestinal tract and increase digestion of the antigens.

As the majority of cases of milk allergy are described as due to the lactalbumin fraction, evaporated milk would appear to be the simplest and most valuable modification.

2. *Milks from other species.*—The lactalbumins of other animals have been found to differ somewhat in their immunology from those of cow's milk and have been used in cases of allergy to the latter. Goat's milk and mare's milk are apparently the most commonly used though many others have been tried (Glaser, 1956). Hill (1955) found that goat's milk was of no value in eczema though it might be of use in gastro-intestinal allergy and cases of acute anaphylaxis.

These substitute milks may fail however, especially if there is a sensitivity to casein, which is not only heat stable but does not vary in its antigenic properties between the different animals' milks used. If a case of cow's milk allergy has failed to respond to evaporated milk or goat's milk, then substitute hypoallergenic milks can be tried.

3. *Hypo-allergenic milks.*—These are usually either:

1. Hydrolysed casein preparations such as Nutramigen (Mead Johnson).
2. Soy bean preparations:
 - (a) Sobee (Mead Johnson) (Hill and Stuart, 1929), which is a liquid preparation now containing soy bean flour, dextrimaltose, soy bean oil, calcium carbonate, salt, chondrus extract and vitamins A and D (Glaser, 1956).
 - (b) Mull-Soy (Borden) which is liquid soy bean flour, without added vitamins (Glaser, 1956).
 - (c) Soyolac etc.
3. Meat base milks (Gerber) in which the strained meat acts as the protein base. Glaser (1956) prefers lamb, but suggests a trial of whale!
4. Other protein bases, such as almonds.

Criticism of these foods in the literature are mainly threefold: Firstly, they may not be tolerated by the infant either because of the taste (Nutramigen has an unpleasant taste) or more seriously because they produce diarrhoea and sore buttocks. This is particularly so with soy bean preparations (Hill 1955), despite claims to the contrary. Glaser found 15% of his series could not tolerate soy bean.

Secondly, the infant may soon show allergic symptoms to the substitute. This is to be expected if one is thinking in terms of an allergic constitution in the individual. Glaser admits that this has occurred even with Mull-Soy. Vest (1935) also reported a case of allergy to soy milk. Allergy to goats milk and to meat base milk and other proteins may sometimes occur.

Thirdly, there are several reports of vitamin A deficiency in Mull-Soy and other substitute milk fed babies. This can, of course, be easily remedied by adding the vitamin, but, if they are used on a large scale, occasional cases are bound to occur due to mistake or carelessness.

Thus the administration of these milks is not without danger, and Glaser admits, in answer to Hill, that infants on these foods must be cared for in clinics experienced in their use. All workers are agreed that the most "hypo allergenic", and tolerated "preparation" of all is human breast milk. There have been in this connection one or two isolated reports of hypersensitivity to human milk. Glaser (1956) has reviewed these, but in a wide experience had not encountered the condition himself.

Conclusion

Cow's milk plays a predominant role in infant feeding. In many countries with the decline of breast feeding, cow's milk is given to an increasing number of infants below 3 months. It is hardly surprising that, in the search for responsible factors in diseases of infancy, allergy to cow's milk has been so often suspected. The proof of its presence has so far been restricted to the "eating thereof", i.e. to the clinical elimination and provocation tests. Skin tests are of no significance in individual cases and no reliable diagnostic im-

munological investigation has so far been produced. Much uncritical work has been done in the past and when this has been combined with enthusiasm, very high incidences of cow's milk allergy have been reported. From the critical work which has appeared the true incidence seems to be relatively rare, probably under 0.5 % of all paediatric cases seen. In "allergic" conditions in which cow's milk appears to be a factor (incidences vary up to 40 %), it is rarely the only one. No critical analysis of the true incidence of cow's milk allergy in countries other than America can be found.

There is enough evidence to show that, in severe allergic conditions in infancy which have proved resistant to the usual methods of treatment, and in which human breast milk is unavailable, a strict therapeutic test of hypo-allergenic substitutes is worth while. This should be done under strict medical observation. As most of the cases are allergic to the lactalbumin fraction only, evaporated milk or goat's milk should be tried first. According to the majority of reports this treatment is sufficient in most allergic conditions based on cow's milk. If marked relief does not occur within two weeks then a completely cow milk and casein free diet should be tried using proprietary hypo-allergenic preparations such as meat bases or soy bean soups. If no marked relief is obtained within a further two weeks, then cow's milk is probably not a factor of importance in the condition and can be recommenced. Relief which is obtained by these methods often proves to be only temporary (Meyer, 1952), possibly due to the formation of the new antibodies. If relief continues, then cow's milk should be reintroduced as soon as possible after the allergic condition has

cleared or become stabilised, the rate at which this is done depending on the reappearance and intensity of the original allergic symptoms. According to most reports this has been done within three or four months of the initial removal of cow's milk.

In the occasional severe case of anaphylaxis, which should, if possible, be proved by an ingestion test of homeopathic quantities of cow's milk, a completely cow milk free diet may be necessary. Similarly infants with gastro-intestinal disturbances which can be proved to be due to intolerance to cow's milk may require this treat-

ment also. Some of these cases are sensitive to the lactalbumin fraction only and thus may tolerate evaporated milk or goat's milk.

To this limited extent, then, there is a need for hypo-allergenic milk preparations or substitutes. As regards the future it is more likely that discoveries concerning the basic conditions of allergy and anaphylaxis will remove the need for finding and excluding the specific "allergens" (in the condition under discussion, cow's milk), than that cow's milk will be found to play any larger a part in allergic conditions than has already been suggested.

Summary

The condition of sensitivity or allergy to cow's milk in infancy is reviewed. The terms "sensitivity" and "allergy" have been used almost synonymously, though this may not necessarily be correct. No definite correlation between clinically suspected cases and the experimental demonstration of an abnormal antigen-antibody response to cow's milk has been found. The clinical diagnosis and the significance of the immunological findings is discussed.

The reported incidence of cow's milk allergy in general paediatric practice ranges from 0.3 % to over 7 %. This variation is thought to be due to the criteria used in diagnosis and the population of allergic cases in the series reviewed. Similarly the importance of cow's milk in recognised allergy in infancy is differing suggested, but is probably small.

The methods of treatment in conditions in which cow's milk allergy is suspected of being a factor are reviewed. Hypo-allergenic substitutes for cow's milk are compared. In conclusion, the need for critical observation of cases thought to be "sensitive" or "allergic" to cow's milk is emphasised and a scheme of treatment suggested.

Rapport sur l'allergie chez l'enfant, causée par le lait de vache.

On rapporte l'état d'une sensibilité ou d'une allergie chez l'enfant, causée par le lait de vache. Les expressions « sensibilité » et « allergie » ont été employées presque comme synonymes, bien que ceci ne soit pas tout-à-fait juste. On n'a pas trouvé de corrélation déterminée entre les cas suspectés cliniquement et la recherche expérimentale d'une réponse anticorps-antigène anormale au lait de vache. Le diagnostic clinique et l'importance des recherches immunologiques sont discutés. L'incidence rapportée de l'allergie due au lait de vache dans la pratique générale en pédiatrie varie de 0,3 % jusqu'à plus de 7 %. On pense que cette variation est due aux critères employés dans le diagnostic et à la population des cas allergiques dans la série rapportée. De même, dans l'allergie reconnue chez l'enfant, l'importance du lait de vache est suggérée différemment, mais celle-ci n'est probablement pas

considérable. On rapporte les méthodes de traitement dans les états où l'allergie due au lait de vache est suspectée en être le facteur. Les succédanés hypoallergéniques pour le lait de vache sont comparés. Pour conclure, on souligne la nécessité d'une observation minutieuse de cas suspectés d'être « sensibles » ou « allergiques » au lait de vache et l'on suggère un schéma de traitement.

Ein Übersicht über die Kuhmilch-Allergie im Säuglingsalter

Der Zustand der Überempfindlichkeit oder Allergie gegenüber der Kuhmilch in der Kindheit wird überprüft. Die Ausdrücke „Überempfindlichkeit“ und „Allergie“ sind meist sinnverwandt gebraucht worden, obwohl dies nicht notwendigerweise richtig sein muss. Es ist keine bestimmte Beziehung zwischen klinisch verdächtigen Fällen und der experimentellen Demonstration einer abnormalen antigenen Antikörper-Gegenwirkung gegenüber der Kuhmilch gefunden worden. Die klinische Diagnose und Bedeutung der immunologischen Entdeckung wird besprochen. Der gemeldete Einfluss von Kuhmilch-Allergie in der allgemeinen Kinderpraxis beläuft sich von 0,3 % bis über 7 %. Diese Verschiedenheit muss an die Kennzeichen, welche bei der Diagnose und bei der Veröffentlichung der allergischen Fälle, die in Gruppen überprüft worden sind, zugeschrieben werden. Ähnlich wird der Einfluss der Kuhmilch bei anerkannter Allergie während der Kindheit abweichend angedeutet, doch ist er wahrscheinlich klein. Die Behandlungsmethoden in Fällen, in welchen Kuhmilch-Allergie vermutet wird oder einen Faktor dabei darstellt, werden überprüft. Hypoallergische Ersatzmittel für Kuhmilch werden verglichen. In der Schlussfolgerung wird die Notwendigkeit für kritische Beobachtungen der Fälle die als überempfindlich oder allergisch auf Kuhmilch angenommen werden, nachdrücklich betont, und ein Behandlungsschema wird vorge-schlagen.

Revisión de la alergia por leche de vaca en la infancia.

Se revisa la sensibilidad o alergia a la leche de vaca en la infancia. Los términos « sensibilidad » y « alergia » se han empleado casi como sinónimos, aunque ello no sea absolutamente correcto. No se ha observado una correlación definida entre los casos sospechados clínicamente y la demostración experimental de una respuesta antígeno-anticuerpo anormal a la leche de vaca. Se discute el diagnóstico clínico y la significación de los hallazgos inmunológicos. La incidencia de la alergia a la leche de vaca en la práctica pediátrica general oscila de 0,3 % a más del 7 %. Esta variación se cree que es debida a los criterios en que se apoya el diagnóstico y en la población de los casos de alergia de las series revisadas. Del mismo modo se sugiere la importancia de la leche de vaca en el diagnóstico de la alergia en la infancia, aunque es probablemente escasa. Se revisan los métodos de tratamientos en los procesos en los que se incriminan como factor responsable la alergia a la leche de vaca. Se comparan los sustitutivos hypoalergénicos para la leche de vaca. En resumen se insiste en la necesidad de la observación crítica de los casos que se suponen con sensibilidad o alergia a la leche de vaca sugiriéndose un esquema del tratamiento.

Addendum

Since this review was written Ratner and his co-workers have published further important studies on the anaphylactogenic properties of highly purified cow's milk proteins. These suggest that the lactoglobulin fraction, which is partially heat labile, is a more potent allergen than lactalbumin and may be responsible for the majority of cases of milk allergy.

(Ratner, B., Dworetzky, M., Oguri, S., & Acheheim, L.: Studies on the allergen-

icity of cow's milk. I. The allergenic properties of α -casein, β -lactoglobulin and α -lactalbumin. II. Effect of heat treatment on the allergenicity of milk and protein fractions of milk as tested in guinea pigs by parenteral sensitisation and challenge. III. Effect of heat treatment on the allergenicity of milk and protein fractions of milk as tested in guinea pigs by sensitisation and challenge by the oral route. Pediatrics, 22: 449, 648, 653, 1958).

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Pediatric Clinic
Akademiska sjukhuset
Uppsala
Sweden

PROCEEDINGS OF PEDIATRIC SOCIETIES

Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting April 11, 1958

G. Hedenström and G. Hult: Frequency of positive toxoplasma titers among women of childbearing age in Jämtland province during 1955

Six hundred and fourteen women admitted to the Maternal Health Center and to the Lying-in Hospital in Östersund during 1955 were examined for toxoplasma antibodies in the blood. The average frequency of positive titers was 33.2%. This rose with increasing age from approximately 25% between 15 and 20 years of age to about 50% at 40 years of age. The test titers were mostly low, 1/10 and 1/50. Most cases suggested the presence of an older toxoplasma infection in the healing stage. Among 72 farmer wives, 41.7% gave positive titers. Their average age, however, was higher than for the total material. Among women with toxoplasma antibodies, 16.3% had aborted at some time as against 7.5% among the negative group. In the former 7.7% of the pregnancies terminated with abortion as against 3.7% among the latter. No difference existed in the frequency of stillbirths.

S. Aleman, L. A. Carlsson and G. Sterner: Familial juvenile hypercholesterolemia

A preliminary report deals with a mother and her two daughters, aged 9 and 12 years, who presented essential hypercholesterolemia. Mostly the mother, but also her oldest daughter had typical xanthoma tendinosum, while the youngest daughter had only hyper-

cholesterolemia. Corn-oil effected a fall in their serum cholesterol levels. More complete examination results will be published later following a longer observation period.

P. Nordenfelt: Children and film

P. O. Rudert: Chronic hemorrhagic anemia arising from telangiectasies in the small intestine

A 10½ year old boy suffered since 1 year of age with chronic, during later years a grave, anemia for which he had been admitted 8 times in the hospital since he was 5½ year old. The total hospital stay exceeded 1 year. Examinations revealed regularly an iron deficiency anemia due to gastro-intestinal hemorrhage. An abnormal hemorrhagic diathesis had never been demonstrated and a localized process in the gastro-intestinal tract had therefore been suspected. Despite some 20 x-ray examinations, repeated proctoscopy, and an explorative laparotomy, no hemorrhagic source had ever been disclosed. During the years the boy had received large amounts of iron and repeated blood transfusions. Finally two circumstances hastened a second laparotomy. After the last blood transfusion he had partly sustained a threatening hemolytic reaction due to cold agglutinins, partly the bone-marrow had begun to display certain exhaustion symptoms in form of leucopenia and thrombocytopenia trends. During the second laparotomy the level of the hemorrhagic source could be localized by means of

the appearance of dark blood in the colon and the lower portion of the small intestine. In the upper portion of the jejunum a 5 cm long area of the intestinal wall revealed a rich network of superficial, tortuous and thinwalled vessels. A resection was made of this area. The subsequent clinical course was smooth. The boy remained free from symptoms as late as 1 year after the operation. The histo-pathologic examination revealed telangiectasises of the type occasionally observed in Morbus Rendu-Weber-Osler.

Blood-vessel tumors in the digestive tract are rare, and yet not more unusual than that in the present case with protracted sideropenic anemia and occult hemorrhage from the gastro-intestinal tract, one should bear it in mind. However, the diagnosis is difficult. Intermissions in the hemorrhage add further

obstacle against its ready detection. The simultaneous appearance of cutaneous hemangioma gives a hint about the nature of the hemorrhagic source. Gastroscopy and proctoscopy may clinch the diagnosis. X-ray is usually of little or no aid. In exceptional cases one may meanwhile in hemangioma in the digestive tract find nodular mucous membrane folds, unevenness in contrast, strictures or local dilatations. Occasionally one may encounter phlebolites in cavernous hemangioma in atypical positions within the abdominal area. The exploratory laparotomy becomes not seldom actual as a last differential diagnostic expedient. It should be performed during the ensuing hemorrhage in order that the appearance of blood in the intestine may supply a hint on which level to look for changes in the intestinal wall.

Meeting May 14, 1958

Tore Mellbin: Pyrexia of uncertain origin treated with cortisone

Two cases were reported, one of an 8-year-old girl and one of a 4-year-old boy, with pyrexia of uncertain origin for several months, with normal temperature in the morning and about 40°C in the afternoon. The micro ESR was between 30 and 70 mm, and serum electrophoresis and other laboratory tests, serological tests, bacteriological cultures, and X-ray examinations were normal. Large doses of antibiotics did not change the situation, but when cortisone was administered the temperature became normal and the general condition improved. After the therapy was discontinued, the good results have persisted, and the patients have now remained healthy, the girl for two years and the boy, so far, for 3 months.

S. Edlund: Case of congenital afibrinogenemia

Full-term infant boy weighing 3620 g at birth. Delivery by low forceps because of intra-uterine bradycardia. Mother's health

good during pregnancy. Infant's general physical condition never satisfactory. Umbilical hemorrhage 1 hour after delivery. Spleen not palpable. Petechiae. Thrombocytes count normal. Fresh umbilical hemorrhages 10 hours after birth, as well as bleeding from eyes and mouth. Bleeding-time prolonged and coagulation-time more than 6 hours. No coagulation of patient's citrated plasma after recalcification, either on addition of thromboplastin plus Ca^{++} , or of concentrated thrombin solution. Prothrombin-proconvertin concentration less than 10% but greater than 1%. No demonstrable circulating anticoagulans or fibrinolytic activity. When patient gradually developed signs of shock he was given blood transfusions. When coagulation test showed absence of fibrinogen he was given 750 mg fibrinogen intravenously, upon which the bleedings stopped promptly. Eighteen hours after delivery coagulation-time was 6 min 20 sec; after 36 hours prothrombin-proconvertin concentration was 11% and coagulation occurred in the patient's recalcified citrated plasma. Death took place 36 hours after

delivery. Autopsy revealed terminal haemorrhages, sparse hyaline membranes and smaller hemorrhages in several organs. Thus the patient presented the characteristic clinical and coagulation picture of afibrinogenaemia.

R. Berfenstam and B. S. V. Bille: Smoking during pregnancy and lactation

A questionnaire among mothers revealed that their smoking frequency of 36% before pregnancy was lowered to 26% during pregnancy and to 19% during the nursing period. Corresponding figures for excessive smokers (more than 8 cigarettes daily) were 12%, 6% and 4%. The authors are inclined to subscribe to Emanuel's conclusion that 5-6 cigarettes a day may be a safe margin, but stress that further research is indicated owing to the demonstration of lesions in the foetuses of animals administered nicotine. Further research is also required into the role played by CO₂ produced during smoking in the production of fetal lesions.

Stig Sjölin: Studies on the anaemia of osteopetrosis

The haematological findings in 4 children with malignant osteopetrosis were reported and discussed. It was shown that the main factor responsible for the anaemia was an extra-corpuscular haemolytic process. Because direct and indirect Coombs's tests were

negative, and owing to the thrombocytopoenia that was present in all cases, it seemed likely that the hyperhaemolysis was due to hypersplenism. Splenectomy was performed in all cases. Pronounced improvement in the anaemia was noted in one case, moderate improvement in two cases, while the anaemia was uninfluenced by the splenectomy in the fourth case. The thrombocyte count returned to normal in all cases after operation.

O. Mellander, B. Vahlquist, and co-workers: Breast milk and cow's milk in infant feeding — a clinical, serological, and biochemical study in 402 children

The authors give a brief review of a report under preparation. Some of the results may be summarized as follows. Infants weaned early from the breast gain less rapidly in weight during the first trimester of life, and more rapidly in the second trimester, than breast-fed babies. By the age of 7-8 months children weaned early are slightly but significantly taller and have a greater number of osseous centres than breast-fed babies. These latter have lower serum phosphorus and alkaline phosphatase. In infants weaned early the combined incidence of different types of acute infections, predominantly in the upper respiratory tract, is higher than in the breast-fed babies. In children weaned from the breast before six months of life the level of gammaglobulin is significantly higher than in children weaned after this time.

Meeting Sept. 20, 1958

O. Brandberg: Ulcerative colitis viewed as an internal medical problem

Four children aged 5-14 years with severe ulcerative colitis were treated for some time on specialized diet, with intestinal antiseptics such as salazopyrin and similar preparations, as well as blood transfusions without any effect. The use of cortison products (del-

tacortil, precortalon and lately kenakort) brought about in all cases a remarkable clinical improvement which eliminated the state of invalidism and enabled the patients to resume their schoolwork which had long been interrupted by indisposition, in one case for a whole year. The results were unquestionably satisfactory with reference to subjective improvement and cessation of treat-

blesome state with diarrhea. Rectoscopy and colon roentgenography revealed no improvement. The treatment occasioned in 2 instances (the severest) a mild Cushing's syndrome with facial redness and edema ("moon-face"). These cases are destined to surgery, but such intervention is both invalidating and painful on account of enterostomy with all its disagreeable consequences. The risks of intestinal wall abscess with peritonitis, as well as cancer, stricture of colon, and of intestinal hemorrhages endanger life. Although the cortison treatment may imply the use of magic arts, at least it affords the patients a badly needed respite of time which may prove useful for observations, investigation, psychiatric adjustment and the best possible improvement of the general condition. One may also hope for a reduction in the harmful by-effects of improved future cortison products.

R. Carleson: Ulcerative colitis viewed as a surgical problem

Approximately 20-30% of ulcerative colitis cases require surgical treatment. The *acutely severe fulminating cases* comprise 5% of the total material. Mortality has been high both by surgical and medical therapy, 68% (in the acute phase 36%, in later forms 32%). Considerably better results are obtained when the case is carefully prepared and subsequently operated with total or subtotal colectomy. It seems imperative that the diseased portions of the small or large intestine should be removed. Speedy unprepared surgical intervention should be averted. *Chronic cases* which fail to yield to medical therapy may be restored to a more normal life by ileostomy plus colectomy. In selected cases of children one may spare the rectum and instead resort to colectomy plus ileorectostomy. The follow-up treatment is important. Some *complications* require a more or less speedy intervention, as f. ex. perforation, abscess, fistulae and ileus. Others such as hepatitis, hypoproteinemia and hypoprothrombinemia throw important light on the present status and the hemor-

rhages. Strictures, pseudopolyposis and cancer degeneration were discussed more closely. Strictures arise from cicatricial contraction of connective tissue within and surrounding the intestine and represent organic irreversible alterations; their treatment is operative. Pseudopolyposis is post-inflammatory; it should be placed in the same class as adenomatous polyps of neoplastic origin. Pseudopolyposis occurs in 50-70% of cancer cases. The cancer frequency increases with the duration of the disease whether or not the cases are treated or untreated. The frequency is estimated at 3-11%. In the course of 5-10 years it increases to about 30%. The American figures closely agree with those advanced by Rosenqvist & Lagercrantz. Cancer in younger people under 35 years of age occurs in 60-70%. It is malignant and metastasizes quite early. Mortality is about 85%. Ileostomy alone fails to prevent cancer degeneration.

DISCUSSION.—J. Lind: Lagercrantz has been in the position to closely follow 150 cases of colitis ulcerosa in childhood. It was shown that no case of cancer appeared during the first ten years of the illness but, on the other hand, in cases that were followed for 11-22 years, a cancer frequency of 33.3% was established. Rosenqvist, Lagercrantz and co-workers have collected a material from Karolinska Sjukhuset of 26 cases of verified cancer in colitis ulcerosa patients. Most of these patients had fallen ill in colitis ulcerosa before 15 years of age, and there is an impression that cancer appears more often in patients taken ill in childhood than in those taken ill as adults. When cancer was diagnosed the changes were, as a rule, already highly advanced. During the year following the discovery of cancer, not less than 22 of the patients died. Only 4 were alive at the follow-up examination 1-10 years after the discovery of cancer. The experience that cancer is so highly malignant indicates that the treatment should be planned as a prophylactic operation in which the risk for cancer should be considered as a strong addendum to the other indications of operation. Rosenqvist does not believe that

cancer at colitis ulcerosa, as a rule, is preceded by a formation of polypus. He supports and confirms the important observations by Svartz & Ernberg that the development of cancer often appears in cases that for a long time have been without trouble or almost symptom free. It is probable that by an extended scar (cicatrice) healing, ulceration with hemorrhage and increased mucous secretion cannot appear to the same extent as before. Edling, who cooperates with Rosenqvist & Lagercrantz, states that a difficult fibrotization of the wall of the colon causes a decrease of the length of the whole of colon and can be radiologically visualized, not only as a decrease of the lumen, but as a shortening of the organ as a whole. In 17 of the 26 cases observed, the colon was found much changed and shortened without flexures and with a characteristically oval shape. In by far the greater part of the cases, cancer was developed in the upper part of the colon, wherefore colectomy and anastomosis between ileum and rectum should be considered in such cases.—*B. Vahlquist*: In Uppsala we have in certain cases followed the English example and attempted to treat ulcerative colitis locally with cortison lavage. The results have not been too encouraging. With reference to surgical therapy, its difficulty is to fix the optimum time for the destructive intervention, which should neither be too late nor too early.—*A. Wallgren*: It is a problem to determine when the disease may be considered cured. How long should the symptom-free observation period be? Medical insurance reckons with 5 years and besides requires a normal roentgenogram. Another problem is the cause of the markedly increased frequency of the disease, which is tantamount to the disclosure of the cause of the disease itself. Before this problem is clarified we may not profitably carry on any prophylaxis.—*Th. Ehrenpreis*: Eleven cases of ulcerative colitis (6 boys and 5 girls aged 11–17 years) have been operated upon in the Children's Clinic at the Karolinska sjukhuset. The surgical indication was in 7 instances a long-standing anamnesis of

severe invalidism, strictures in 2 cases and an acute course with peritoneal irritation and risk of perforation in 2 others. In 7 cases the operation consisted of colectomy plus ileostomy, in 6 of which the rectum was left intact and in the remaining case it was primarily extirpated because of excessive involvement. The rectum was normal in the 4 other cases which were treated with subtotal colectomy plus primary anastomosis between the ileum and rectum. The results have been very encouraging. All the patients have survived the operation and the post-operative period without any noteworthy trouble. In our long-term follow-up no contact was made with 1 patient from Finland; in 3 cases the observation lasted less than 6 months. The remaining 7 patients were followed-up from 7 months to 6 years. Within a very short time they regained normal physical and mental health. The most conspicuous traits were considerable gains in weight and elimination of anemic disposition. The stools became semi-solid within a short time, with 3–5 evacuations daily. Ileostomy has been accepted with favour as a price for recovery. The risk of cancer, which Lagercrantz & Rosenqvist stressed as correlated to the length of the anamnesis and to the duration of the pre-cancerous remission, together with the uniformly favorable experience with our surgical material, compel us to formulate more specifically our previous rather vague operative indications as follows: cases presenting surgical complications (perforation or threat of perforation, stricture, diverticulitis, fistule), and cases running an acutely fulminant course which fail promptly to respond to internal medical treatment, and with more than 5 years' anamnesis of residual clinical, rectoscopic or roentgenological manifestations of ulcerative colitis.—*C. G. Bergstrand*: The complications arising from treatment with steroids, which are relatively easy to prevent, are mainly correlated with the "mineralocorticoid" activities of the steroids. These side effects may be reduced or eliminated by inducing certain alterations in the steroid molecule. The more serious complications as f.ex. a malignant course

with a virus infection, appears to be connected with the "glucocorticoid" activities of the steroids. The therapeutic action rests on just such activities. It would seem highly improbable therefore that one should be able to reduce the risk of serious complications without a simultaneous reduction in the therapeutic effect. The expectation of finding steroids which eliminate this form for side effects is scarcely great.—*R. Lundström*: May I ask Dr. Brandberg if he has encountered any of the usual children's infections among his patients while they were undergoing treatment with cortison and if so whether the course of the disease deviated from its normal run? May I also stress that it appears to me justifiable to administer gamma globulin concurrently with cortison, if such is indicated, to compensate for the organism's reduced resistance against certain infectious diseases. Experimental studies of pseudomonas and staphylococcus infections in cortison-treated patients would support such procedure.

E. Rabo: Early smallpox vaccination

The usual vaccination program conducted in Sweden comprises BCG vaccination in the maternity hospitals and the triple DTP vaccination with 3 inoculations after 3 months of age. Smallpox vaccination is supposedly performed sometime between 4 and 12 months of age. However, only 19% of infants were smallpox vaccinated in 1955 and 23% in 1956. For psychological and organizational reasons this program should also include polio vaccination during the first years of life. All vaccinations should be performed as early as possible in order to inflict the least possible mental compunction. In order to spread the overcrowding of required vaccinations during infancy, smallpox vaccination has been performed (by multiple pressure) in the past 2 years during the infant's first visit to the Central Children's Polyclinic, as a rule at 1-2 months of age. Vaccination of 400 infants aged 3-10 weeks produced a positive reaction in 81% while 92% of the control series aged 5-7 months

reacted positively. Noteworthy complications occurred in 8% of infants less than 10 weeks of age as compared to 40% in the older control group. The only drawback of the early vaccination is the relatively lower "take" frequency. However, this is rather of no significance because of the Swedish health control system by which a physician examines the infant regularly at 1-2 months of age. By this vaccination procedure it is easier to space out the remaining required vaccinations in the already positively smallpox vaccinated children. Since children rarely experience local or general vaccination discomforts, the public's opposition to vaccination in general disappears. The mothers take care of the vaccination schedule among themselves. They even insist on getting the remaining vaccinations performed as early as possible. Among 409 infants born in Karlskoga in the interim of September 1, 1956 and August 31, 1957, and who spent the whole first year of life in the town, 63% were successfully vaccinated before 6 months of age and 78% before they reached 1 year of age.

DISCUSSION.—*A. Wallgren*: Is the vaccinia incubation-period the same following vaccination of newborns? One might expect a delayed primary "take" as compared with vaccination of older children. Another pertinent question is whether the degree of immunity is similar to that produced by vaccination of older children.—*N. Malmberg*: First I will answer Professor Wallgren's question about the impact of early smallpox vaccination on the incubation period during the first weeks of the infant's life. My own investigation of such vaccinations, the results of which I laid before the Scandinavian Pediatric Congress in 1934, disclosed no difference whatsoever; the papules and rise in temperature occurred within the same space of time as following vaccination in older children. The formation of pustules and scars, as well as of fever, if any occurred, were meanwhile less strongly marked. If memory doesn't fail me, the percentage of positive "takes" was considerably lower in my material than in that presented by Dr.

Rabo, or only approximately 40%. Even at that time I stressed that an essential part of the result could be occasioned by the highly variable strength of the employed lots of vaccine. F.ex. some lots produced almost 100% positive "takes" while others gave considerably poorer results. In view of the lower percentage of positive primary reactions I considered it justifiable to postpone smallpox vaccination till after 10 weeks of age. If a better and more constant vaccine is available which produces a satisfactory "take" percentage, then it remains merely a question of organization whether one should vaccinate very early or postpone it until the second or third quarter of life. Nevertheless it is important to ascertain whether or not the immunity response is just as powerful following early vaccination as it is at 3-6 months of age.—*B. Vahlquist:* Some time ago I had occasion to show that antibody production during the first period of life is not as mediocre as one had previously presupposed. But a certain difference exists in any case during the first quarter of life, with delayed antibody production and sub-optimum final titre. As Dr. Rabo suggested, one should attempt to combine vaccinations as much as possible in order to reduce the number of obnoxious needle pricks. I am of the opinion that our Health Ministry should unceasingly pursue the immunization questions more vigorously than has been the case heretofore. For instance on the question of the triple DTP vaccination, there is ample opportunity to offer accurate and continuous information to physicians about indications and contraindi-

cations, as well as detailed practical advice about the actual performance of vaccination etc. Many needless complications could thus be averted.—*E. Rabo:* The Dutch author Doorschodt has recently investigated the inhibition of hemagglutination and neutralizing antibodies 3 weeks following smallpox vaccination of children aged 6-14 weeks, 15 weeks-6 months and 6-12 months. The titres were approximately as good in the youngest as in the oldest groups. Thus the immunity response should practically be equivalent in younger and older infants.

***B. Göthman:* A case of esophageal stricture of unusual type; clinical course and surgical treatment**

The case concerns a 3-years-and-8-months-old boy, 12.5 kg, underweight, undernourished, with severe anemia, who since 1½ years of age has experienced difficulty with swallowing, vomiting and regurgitations. Extreme esophageal stricture, hiatus-hernia, brachy-esophagus and pronounced peptic esophagitis were demonstrated. Surgical operation was performed in July 1956: resection of the lower $\frac{2}{3}$ of esophagus and mobilization of stomach in front of the aortic arch for anastomosis with upper end of esophagus. Histopathology: totally destroyed mucous membrane plus marked inflammatory alterations in the entire esophageal wall. Smooth post-operative course, with good passage in the esophagogastric portion. Patient has increased in weight to 18 kg and eats anything without difficulty.

BOOK REVIEWS

Tuberculosis in White and Negro Children. Vol. I. The Roentgenological Aspects of the Harriet Lane Study: Janet B. Hardy. Vol. II. The Epidemiologic Aspects of the Harriet Lane Study: Miriam E. Brailey.

Harvard University Press, Cambridge, Mass., U.S.A., 1958. 122 + 109 pages, numerous figures and tables. Price \$7.50 + 4.50.

The Harriet Lane Tuberculosis Clinic was organized by Dr. Edwards A. Park in the Department of Pediatrics at the Johns Hopkins Hospital in November 1928. The majority of the admitted children were supported by public relief. The difference in the living conditions between White and Negro families was not striking. Antimicrobial therapy was unknown during the period studied. Children who reacted only to 1 mg of O.T. were excluded from the study as non-tuberculous, unless unequivocally positive findings were obtained from X-ray examination.

The two volumes which are published for the Commonwealth Fund are based upon experiences gained during 1928-1944. In 1950 the authors made a follow-up study of the 1329 tuberculous children under 2 years of age admitted to the Clinic; more than two thirds of the children were colored.

The first volume consists of a large number of reproductions of roentgenfilms with brief clinical descriptions showing the roentgenologic development of primary infection in these young children. Most pictures are well printed, but too many are underdeveloped or in other ways not quite satisfactory. Dr. Hardy criticizes Myers' terminology of childhood tuberculosis but she uses his term reinfection tuberculosis, which certainly may lead to confusion. She talks about exogenous reinfection in people with post-primary tuberculosis who have acquired resistance and hypersensitivity. Post-primary "tuber-

culous pneumonia" is also an unfortunate term, because it is prejudicing; it is only in retrospect that it can be decided whether it is atelectasis or real tuberculous lesions. To judge from some of the reported cases post-primary "tuberculous pneumonia" has been labelled also on fresh perifocal primary complex. What is said about the technique and roentgen examination and interpretation of chest roentgenograms corresponds with the experiences of European prediatricians. The first volume closes with brief notes on bronchoscopy and bronchography in children.

Volume two is divided into two sections: The Prognosis of Tuberculous Infection in Children and The Risk of Developing Reinfection Pulmonary Tuberculosis in the Experience of the Harriet Lane Tuberculosis Clinic. In the discussion of the results of the study due consideration is taken to previous publications, especially from Scandinavia, England and the United States. The mortality from tuberculosis was calculated to be about 9% for White children and nearly 22% for the corresponding group of Negro children. Out of 434 infected White children observed for 5930 person-years, only 2 cases of post-primary pulmonary tuberculosis came to light, while out of 858 infected Negro children observed for 9732 person-years, 32 developed progressive pulmonary tuberculosis. The risk was about five times greater for girls than for boys. For each sex the risk of contracting progressive pulmonary tuberculosis within a decade was roughly twice as great if a child was infected between the ages of three and fifteen as it was for a child whose primary infection was discovered before the third birthday. Dr. Brailey believes that in susceptible subjects, notably in children of Negro stock, superinfection increases the risk of the development of phthisis.

This well organized, excellently performed

and perfectly reported study of the course of primary infection gives a fair picture of the fate of tuberculous small children before the advent of the chemotherapeutics and it demonstrates in a very obvious way the im-

portance of natural resistance and susceptibility for the prognosis of the infection. The two volumes are to be regarded as precious documents from a period now passed and should not be missing in any medical library.

ANNOUNCEMENTS

Fellowships

The Nestlé Fellowship

A research fellowship of one million francs is awarded every year by the French Nestlé Company to a physician who wishes to specialize in the field of nutrition. The 1959-1960 fellowship will be awarded in the spring 1959. The applicants are requested to send to the International Children's Centre, Château de Longchamp, Bois de Boulogne, Paris XVI^e:

- a) a *curriculum vitae* setting up forth their work on the biological and social problems connected with feeding or nutrition of infants and children,

- b) an *introduction letter* from one of their Masters

- c) a description of *the studies they wish to pursue* with the help of the fellowship.

The applicants must have a sufficient command of the French language. At the end of the fellowship period, the fellow or fellows will be expected to send to the International Children's Centre a scientific study on the subject which they will have studied during the year.

The Guigoz Fellowship

The 1959-1960 fellowship will be awarded in the spring 1959. The applicants are required to send to the International Chil-

dren's Centre the same documents as for the Nestlé Fellowship.

The *XVII Congress of the Association of French Speaking Pediatricians* will be held in Montpellier with professor Jean Chaptal as President Octobre 12-14 1959. The main subjects to be discussed are: 1. Hypoparathyroidism in infants and children.—2. Jaundice in the neonatal period and in in-

ants.—3. The EEG during the cerebral maturation; physiologic and pathologic aspects. Further information of this Congress may be delivered if requested. The General Secretary is Associate Professor R. Jean, address: 8, Rue Guillaume-de-Nogaret, Montpellier, France.

An Attempt with STH-Treatment in Chondrodystrophic Dwarfism

by GUNNAR W. MEEUWISSE

Fetal chondrodystrophy or achondroplasia is a hereditary disease affecting the fetus and often well recognizable at birth. The pathological changes persist throughout life. Because of the low fertility of the afflicted individuals, the defective gene soon dies out. Most of the chondrodystrophic dwarfs are born to normal parents, but they possess a gene anomaly, the result of a spontaneous mutation (15, 20).

By coincidence three chondrodystrophic newborns were admitted to the Pediatric Department of the Boden Central Hospital (in the very Northern part of Sweden) within the period of half a year. As we hoped to induce a better growth of the long bones of these patients, they were treated with hypophyseal growth hormone (STH).

The STH used in our cases was derived from the oxycellulose filtrate from hog pituitaries by a modification of the method of Raben and Westermeyer (18). The preparation is called "Somacton" (Ferring).¹ STH was previously used at our hospital in the treatment of epidermolysis bullosa and, as it seemed, not unsuccessfully and without side effects (5).

Case Reports

Case A. Male, second of two children with normal parents and no heredity of dwarfism. His mother was healthy during pregnancy. Pat. weight at birth: 4.450 g. Length: 54 cm. The first time the patient was admitted to the Hospital was at the age of five months. He then possessed the typical symptoms of chondrodystrophy. He was treated with daily injections of STH, 500 tibia units intra-muscularly in periods of 30 days at the ages of 5, 9, 13 and 17 months. For this purpose he was hospitalized at the same periods. At the Hospital and at home, whether he did or did not receive STH, he had irregular feverperiods to 38–39°C of unclear etiology. As is often observed in fetal chondrodystrophy, static and motor development was poor. The patient began to talk at one year, but at 1½ the speech development tended to slow down.

Case B. Male, first and sole child of a 32-years-old mother after 3 abortions. This case has special interest because the mother belongs to the extremely rare blood group anti-Tj^a, known to be combined with habitual abortion. Regarding her case history she was prescribed total rest during nearly the whole period of pregnancy. The boy was born 2 weeks after calculated time and weighed 2.470 g at a length of 40 cm. He

¹ The preparation "Somacton" was put to our disposal by Ferring Ltd, Malmö.

had short arms and legs, indicating fetal chondrodystrophy. Later on the symptoms became very clear also on the roentgenograms. The somatic development was slow. At the age of 14 months he still could not balance the skull. At this age we lost sight of him, but he was admitted to the Pediatric Clinic at Lund because of lasting, irregular fever that did not respond to therapy. Finally the fever was interpreted as cerebral fever. Encephalography revealed cerebral atrophy. The physicians got the distinct impression that the patient was mentally retarded, which is not a rule in fetal chondrodystrophy.¹ This patient was treated with STH, 250 tibia units daily in periods of 30 days, nearly immediately after birth, at the age of 2 months and finally at the age of 5 months with 500 units daily. In this case it is unclear whether the mother's blood anomaly has anything to do with the genesis of the patients chondrodystrophy.

Case C. Female, number 7 of eight children. All the others normal and healthy. The patient was born 20 days before calculated time and weighed 1.400 g. Length: 36 cm. The typical malformations of chondrodystrophy were immediately recognised. After a week a cardiac murmur could be heard which grew in intensity later on. She received 250 tibia units STH daily in two periods of 30 days at the ages of 2 and 8 months.² Renewed examination of the roentgenograms recently revealed, that this little patient did not suffer from the ordinary form of fetal chondrodystrophy, but from chondrodystrophy combined with "stippled epiphyses", chondrodystrophia calcificans congenita or as it is also called: chondroangiopathia calcarea s. punctata (4). This disease is very rare (19, 20). Only 3 cases previously have been described in Sweden (2, 11). Other malformations, such as congenital heart disease are frequent in this entity.

Methods

The patients were followed during and after therapy until the age of 13–22 months. Measurements were made of the lower extremities (the distance between the ventral iliac spine and the internal malleolus) and of total length. Roentgenograms were made at several times. Due to difficulties in getting the infant's legs completely straightened, measuring the roentgenograms was by no means a better method to achieve exact figures of the length of the lower extremities than measuring directly on the infant.

Results

Fig. 1 refers to the growth of the three patients in comparison with normal infants. The curves in the upper part of the diagram refer to total length. In the lower part the

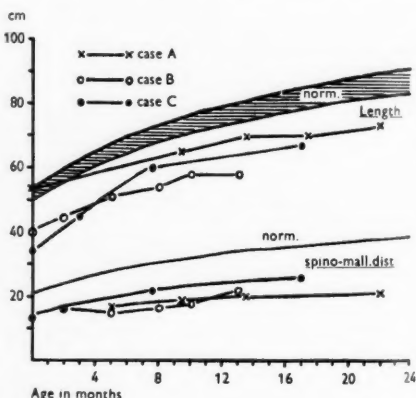


Fig. 1. Growth curves of three chondrodystrophic dwarfs treated with STH, compared with normal growth. The curve of normal length $\pm \sigma$ and $-\sigma$ is according to Karlberg and Perman. The normal spino-malleolar distance is obtained by adding 14–4 cm (which is the difference between spino-mall.dist. and symphysis height) to Holt's and McIntosh' (10) values for symphysis height in normal children.

¹ With acknowledgment to the Pediatric Clinic at Lund for the latest data.

² With acknowledgment to the Pediatric Department, Västerås, for the latest data in this case.

length of the inferior extremities is shown, also in comparison with normal infants. Considering only the total length, the growth is not so evident because of normal length of the trunk, which is often even too long initially, as in Case A, who at birth had a normal length, but very short extremities.

It is easily seen from the digram that we did not succeed in achieving an accelerated growth of the legs. Those of Case A grew 4 cm between 5 and 22 months of age, against 10 cm normally. Case B: 6 cm between 2 and 13 months. Normal value: 11 cm. Case C: 13 cm from birth untill 17 months. Normal value: 15 cm.

Discussion

The failure of this treatment would perhaps have been more impressive if figures on the growth of untreated chondrodystrophic dwarfs were available. However, such figures were not at our disposal. Otherwise they would be of no great use, because there are many grades of fetal chondrodystrophy, the one much graver than the other. Mild forms do grow a great deal. Pat. C grew better than the others but at the age of 17 months the legs were still disproportionally short. However, this patient suffered from "stippled epiphyses" and it is known that in this condition growth is pretty good. The characteristic lesions at the roentgenograms disappear sooner or later. Note, however, that she received much smaller amounts of the STH than the other two

patients. Case A, who was tallest at birth and received the highest dosage of the STH preparation grew less than B and C.

During therapy none of the patients showed any signs of intolerance to STH. Glycosuria was not observed in any of the cases, nor at the end of the follow-up. The blood glucose levels were always normal. Detailed studies of nitrogen- and ionic balance during STH administration were not made.

The poor results of this attempt to treat chondrodystrophic dwarfism with STH can be due to several factors.

1°: There is no evidence that fetal chondrodystrophy, which depends on very early fetal malformations, is due to lack of STH. However, an attempt was considered justifiable because no complications had occurred in previous treatment of children with the same preparation.

2°: During the last years many reports have been published in which STH prepared from animals proved to be unsuccessful in man. Human STH and monkey STH evidently had metabolic effects in man (1). Physical and chemical differences between STH preparations from different sources have been reported (6, 9, 12), but the hormone is probably not highly specific, in any case not in rats. Ox STH has an effect in rats, and Li et al. could split off notable parts of the ox STH molecule without disturbing this effect (14).

Summary

A short description of chondrodystrophic dwarfism is given. Two new cases of fetal chondrodystrophy and one case of "chondrodystrophia calcificans congenita" (stippled epiphyses) are reported. They were all treated in early infancy with STH derived from hog pituitaries, using doses of 250-500 tibia units daily for 30 successive days. Regarding

the growth of the extremities, the treatment proved to be ineffective in these three cases. Side effects of the STH preparation were not seen either.

Un essai de traiter le nanisme chondrodystrophique avec le STH.

On donne une brève description du nanisme chondrodystrophique. Deux nouveaux cas de chondrodystrophie foetale et un cas de « chondrodystrophia calcificans congenita » (épiphyses pointillées) sont rapportés. Ils étaient traités dans la première enfance avec du STH provenant d'hypophyses de porc, en employant des doses de 250-500 unités par jour dans le tibia, et en répétant ce traitement pendant 30 jours successifs. En ce qui concerne la croissance des extrémités, le traitement s'est avéré inefficace dans ces trois cas. On n'a pas constaté non plus d'effet secondaire de la préparation STH.

Ein Versuch mit STH-Behandlung bei Chondrodystrophischem Zwergwuchs.

Eine kurze Beschreibung über chondrodystrophischen Zwergwuchs wird gegeben. Zwei neue Fälle foetaler Chondrodystrophie und ein Fall von „Chondrodystrophia calcificans congenita“ (punktierte Epiphysen) werden berichtet. Sie wurden alle im frühen Säuglingsalter mit STH, welches aus Schweine-Zirbeldrüsen gewonnen wurde, behandelt, unter Gebrauchmachung von Dosen von 250-500 Tibia-Einheiten und zwar täglich wiederholt in 30 aufeinanderfolgenden Tagen. Hinsichtlich des Wachstums der Extremitäten erwies sich die Behandlung als unwirksam in diesen 3 Fällen. Nebenwirkung der STH-Zubereitung wurden niemals gesehen.

Ensayo del tratamiento con hormona somatotropa en el enanismo condrodistrófico.

Se da una breve descripción del enanismo condrodistrófico. Se aportan dos nuevos casos de condrodistrofia fetal y un caso de « condrodistrofia calcificante congénita ». Todos ellos fueron tratados en la primera infancia con hormona somatotropa obtenida de hipófisis de cerdo a la dosis de 250-500 unidades tibia diarias repetidas durante treinta días. El tratamiento se demostró ser ineficaz en los tres casos, en cuanto al crecimiento de las extremidades. No se observaron efectos colaterales de la hormona somatotropa.

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Pediatric Department
Centrallasarettet
Boden. Sweden.

Respiratory Studies in Children

VI. Timed Vital Capacity in Healthy Children and in Symptom-Free Asthmatic Children¹

by INGA ENGSTRÖM, FLORENÇO E. ESCARDÓ, PETTER KARLBERG
and SVEN KRÆPELIEN

Determination of the ventilatory capacity can reveal the presence of bronchial obstruction in cases with bronchial asthma. Measurement of the vital capacity (V_{VC}) alone does not provide sufficient information, since the time factor is not taken into account. The maximal breathing capacity (MBC), on the other hand, provides a direct expression for the ventilatory capacity. The latter determination is attended by certain disadvantages, however, especially in children as was pointed out in an earlier study in this series (7). It is often replaced by an analysis of a single forced breath, taking into account the time factor (8, 11, 16, 17). Tiffeneau *et al.* (16, 17) and Gaensler (8) suggest measuring the volume expired during the first second of a forced expiration after a maximal inspiration. This measurement is referred to in French literature as "capacité pulmonaire utilisable à l'effort (CPUE)" and in English as one-second capacity (V_{1sec}). It has proved to be well correlated to MBC and gives a good idea of the ventilatory capacity. The

ratio V_{1sec}/V_{VC} has also proved of great value for assessment of the ventilation, especially in asthmatics. In asthmatics the V_{1sec}/V_{VC} ratio, like the V_{1sec} measurement alone, is lowered as expression of bronchial obstruction (4, 5, 8, 14, 15). Similar studies of children are sparsely represented in the literature. van Gelderen (9) has given normal values for the ratio V_{1sec}/V_{VC} in healthy children, and Drutel (3) values of V_{1sec} both in healthy and in asthmatic children.

Since our previous investigations have led us to believe that bronchial obstruction exists in asthmatic children even during symptom-free periods, we decided to use this method with a view to casting further light on the question. At the same time we examined a control group of healthy children by the same method.

Material

The healthy group included 17 children (8 boys and 9 girls) aged 7-12 years, and the group of symptom-free asthmatic children

¹ Aided by a grant from the Swedish National Association against Tuberculosis and Other Social Diseases.

consisted of 38 children (25 boys and 13 girls) from 6 to 14 years of age. The physical development of all the children conformed with the normal values for Swedish children given by Broman, Dahlberg & Lichtenstein (1). The asthmatic children were clinically well known, and were selected in the same way as in earlier publications in this series (7, 12). As previously, the children were clinically classified in three groups according to the frequency of the attacks (Group I: mild asthma with less than 5 short attacks a year, 18 cases. Group II: moderately severe asthma with 5-10 attacks a year, 10 cases. Group III: severe asthma with more than 10 attacks a year, or prolonged status asthmaticus, 10 cases). All the cases had been free of symptoms for at least 3 days before examination, and during this period were not given any symptomatic treatment.

Method

Apparatus.—This consisted of a set-up for recording breathing volume which had been used for the study of the mechanics of breathing in older children. The recording principle is that of the "reverse plethysmograph" described in connection with studies in newborn infants (10). The schematic diagram in Fig. 1 shows the apparatus used. With the nose closed with a nose-clip, the child breathes freely through a mouthpiece and a 35 mm tube into a large air-tight wooden box with a volume of about 1500 litres. The pressure changes inside the box,

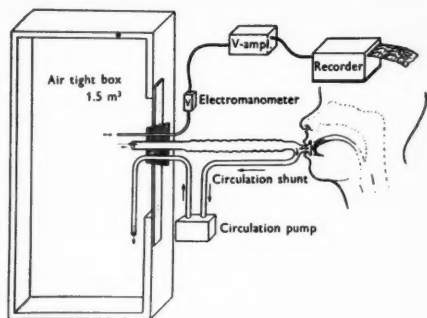


Fig. 1. Diagram of apparatus.

due to the child's breathing, are picked up by an electromanometer (Elema). To avoid re-breathing of air in the tube, a circulation shunt with a membrane pump, which causes no interfering pressure fluctuations in the closed system, goes from the mouthpiece to the bottom of the box.

The amplified signals from the electromanometer are recorded on a direct writing recorder (Elema's Mingograph). For the reproducibility and calibration see the method for newborns (10).

The volume recording system has a low air-flow resistance and is correct in amplitude and phase. The pressure changes inside the closed system are within ± 1 cm H₂O.

Procedure.—The child, in a sitting position and breathing quietly, is strongly encouraged to make first a maximum inspiration and then a forced maximum expiration. Two

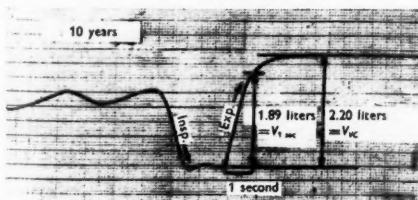


Fig. 2. A record from a 10-year-old healthy girl.

$$\frac{V_{1 \text{ sec}}}{V_{VC}} = \frac{1.89}{2.20} = 0.86.$$

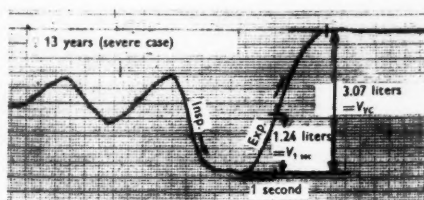


Fig. 3. A record from a 13-year-old girl with a

severe asthma bronchiale. $\frac{V_{1 \text{ sec}}}{V_{VC}} = \frac{1.24}{3.07} = 0.40.$

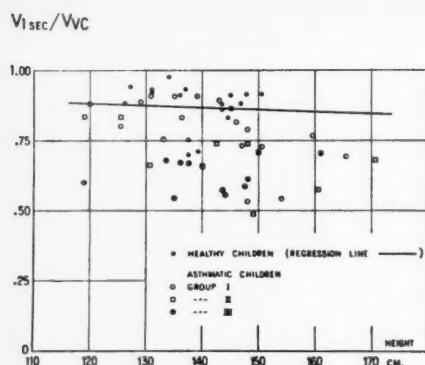


Fig. 4. The ratio $V_{1\text{sec}}/V_{\text{VC}}$ in relation to body height on a metric scale.

typical records are seen in Figs. 2 and 3. This procedure is repeated three to five times at intervals of about one minute.

Calculations.—The two curves with the highest vital capacity (V_{VC}) are selected. As the recording paper runs at a calibrated speed, the volume of air moved during the first second of expiration ($V_{1\text{sec}}$) and the

TABLE 1. *The random error of the method of determining vital capacity (V_{VC}) and ratio $V_{1\text{sec}}/V_{\text{VC}}$. (Volumes in litres.)*

	V_{VC}	$V_{1\text{sec}}/V_{\text{VC}}$
Number of double determinations	55	55
Mean difference (\bar{d})	0.005	0.0024
Standard deviation of the differences (σ_d)	± 0.111	± 0.046
Error in the mean difference (ϵ_d)	± 0.015	± 0.0062
$t = \bar{d}/\epsilon_d$	0.33	0.39
P	> 0.2	> 0.2
Standard deviation in an individual determination (σ_x)	± 0.078	± 0.033
Mean of all double determinations (\bar{x})	2.19	0.767
Coefficient of variation ($\sigma_x \times 100/\bar{x}$, %)	± 3.6	± 4.2

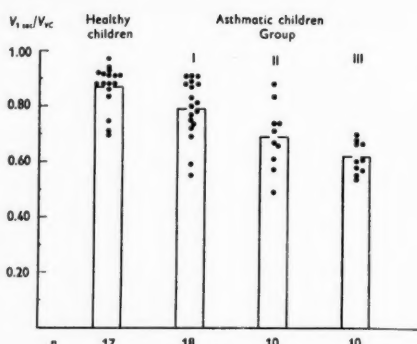


Fig. 5. The mean values of the ratio $V_{1\text{sec}}/V_{\text{VC}}$ in healthy children and in the three groups of asthmatic children.

ratio $V_{1\text{sec}}/V_{\text{VC}}$ can easily be calculated (Figs. 2 and 3). The volumes obtained are corrected to BTPS. The mean value of the two ratios is taken.

Random error of the method.—For the vital capacity, and for the ratio $V_{1\text{sec}}/V_{\text{VC}}$ the random error of the method has been calculated from the differences in 55 double determinations according to Dahlberg (2); (see Table 1). As no training effect was found (no significant difference between the two determinations in chronological order), the mean of the two selected determinations was used.

The coefficient of variation for V_{VC} in this method was found to be of the same magnitude as in earlier studies when using a spirometer. For the ratio $V_{1\text{sec}}/V_{\text{VC}}$ the coefficient of variation was ± 4.2 per cent.

Results

The figures obtained by this method for V_{VC} (in relation to height) are with a few exceptions within 95 per cent confidence intervals for V_{VC} found in earlier examinations of healthy children by the spirometric method (6).

The computed figures for the ratio $V_{1\text{sec}}/V_{\text{VC}}$ have been plotted in Fig. 4 in relation to height (metric scale), the healthy children and the different groups of symptom-free asthmatic children being marked differently. No differentiation has been made between the sexes.

In the group of healthy children the linear regression according to height was calculated, giving the equation $y = -0.00073x + 0.97$ ($y = \text{ratio } V_{1\text{sec}}/V_{\text{VC}}$ and $x = \text{height in cm}$). In order to judge the correlation with height, the slope of the regression line was tested against 0. Since no significant difference was found ($P > 0.2$), the mean value of the ratio $V_{1\text{sec}}/V_{\text{VC}}$ was calculated for the entire group, being 0.869 for the healthy children ($\sigma = \pm 0.079$) with a lower limit for the 95 % confidence interval of 0.702. We did not enlarge the control group as the values of our 17 healthy children correspond with those reported in normal children (van Gelderen 0.822) and adults (Gaensler 0.827, Drutel *et al.* 0.845).

The symptom-free asthmatic children generally show values lower than those found in healthy children. Since the value of the ratio $V_{1\text{sec}}/V_{\text{VC}}$ was not found to be related to height, the material was divided into three groups according to the severity of the asthma judged by the frequency of attacks. The lowest values are found in the group with highest attack frequency (Fig. 5). The mean values are 0.793 for Group I, 0.691 for Group II, and 0.620 for Group III. The differences between these values severally, and between them and the values for healthy children, have been judged by *t*-test (Table 2). A significant difference exists between Group III on the one hand and Group I and healthy chil-

TABLE 2. The mean values of the ratio $V_{1\text{sec}}/V_{\text{VC}}$ in the healthy children and in the three groups of asthmatic children. *t*-test of the differences between the four groups.

Healthy children	Group of asthmatic children		
	I	II	III
17	18	10	10
0.869	0.793	0.691	0.620
$\sigma \pm 0.079$	± 0.106	± 0.118	± 0.057
$\varepsilon \pm 0.019$	± 0.025	± 0.037	± 0.018
<i>t</i> -test	I	II	III
Healthy children	$t = 1.73$ $P > 0.05$	$t = 3.39$ $0.02 > P > 0.01$	$t = 5.78$ $P < 0.001$
Asthmatic children Group I		$t = 1.59$ $P > 0.05$	$t = 3.04$ $0.02 > P > 0.01$
Asthmatic children Group II			$t = 1.28$ $P > 0.05$

dren on the other, and also between Group II and healthy children. Both in Groups I and II, however, there are individual cases with normal ratios. In Group III, on the other hand, there is no case with a ratio exceeding 0.70.

Discussion

The quantity of air forcedly expired during the first second after a maximal inspiration is an expression for an individual's ventilatory capacity, as first pointed out by Tiffeneau & Pinelli (16). This volume, $V_{1\text{sec}}$, depends partly on the size of the individual and partly on obstructive and restrictive impediments to breathing (4, 8). If $V_{1\text{sec}}$ is put in relation to V_{VC} , the resulting value is not appre-

ciably influenced either by the size of the individual or by restrictive impediments to the breathing, since these two factors affect both V_{VC} and V_{1sec} . The bronchial obstruction, however, affects V_{1sec} to a higher degree than V_{VC} , so that their ratio provides a truer expression for the influence of obstructive factors on the breathing (4, 8). In assessing the pulmonary function of asthmatics, therefore, this ratio is of greater interest than the respective volumes independently.

In the course of our work we have found that the determination of V_{1sec} is easily performed on children and that the ratio V_{1sec}/V_{VC} is well reproducible within a random error of the method of $\pm 4.2\%$. Our ratios determined on healthy children coincide closely with those reported in other studies of children and adults.

The results obtained for the symptom-free asthmatic children, with statistically significant lowering in the two groups with higher frequency of attack, show that asthmatic children, even during symptom-free intervals, may have signs of a bronchial obstruction which assumes greater severity the more frequent the asthmatic attacks. These findings coincide with the signs of hyperinflation in symptom-free asthmatic children, as shown by us earlier

(12) and support the evidence presented in an earlier paper in this series, namely, that the hyperinflation in symptom-free asthmatic children is at least partially dependent on a bronchial obstruction (13).

The determination of timed vital capacity has proved to be well adapted for assessing the ventilation in the individual case.

In the study reported above very accurate and sensitive apparatus has been used for determining the timed vital capacity. For clinical assessment of the individual cases we have simplified the method by employing the spirometric system used in lung volume determinations (6, 12). The deflection of the spirometer is recorded on a kymograph with high and constant speed (14 mm/sec), which enables an analysis to be made of the individual breath. The timed vital capacity of 22 children (11 healthy and 11 symptom-free asthmatic children) was determined by both methods in immediate succession (in the first examination with one method applied first, and in the next the other, and so on). A statistical analysis of the results has shown good agreement between the values obtained by the two methods, but with a tendency to slightly lower values for the spirometric method at low ratios of V_{1sec}/V_{VC} . The difference between the two methods is, however, not great and the spirometric method may be considered fully usable in clinical work.

Summary

1. The ratio between one-second capacity and vital capacity, V_{1sec}/V_{VC} , has been determined on 17 healthy children aged 7-12 years and on 38 symptom-free asthmatic children aged 6-14 years.

2. The ratio V_{1sec}/V_{VC} is independent of body size, with a mean value of 0.869 for healthy children, which shows close agreement with the values found by other authors both for children and adults.

3. The symptom-free asthmatic children generally give lower values as a sign of bronchial obstruction. The ratio V_{1sec}/V_{VC} shows good correlation with our clinical

classification of the asthmatic patients, i.e. those classified as severe (Group III) significantly have the lowest values, while the other cases show results closer to the control group.

4. A low value of the ratio $V_{1\text{sec}}/V_{\text{VC}}$ may be used as an expression for bronchial obstruction.

5. The procedure is simple, takes very little time, and is of minimum annoyance to the child.

Etudes de la respiration chez l'enfant. VI. Capacité pulmonaire utilisable à l'effort chez l'enfant normal et chez l'enfant asthmatique, sans symptôme respiratoire.

Le rapport entre la capacité pulmonaire utilisable à l'effort et la capacité vitale CPUE/CV a été étudié chez 17 enfants normaux âgés de 7 à 12 ans et chez 38 enfants asthmatiques âgés de 6 à 14 ans, sans symptôme respiratoire. Le rapport CPUE/CV est indépendant de la taille corporelle du sujet. Sa valeur est de 0,869 chez les enfants normaux — ce qui est en parfait accord avec les résultats fournis par d'autres auteurs tant en ce qui concerne les enfants que les adultes. Les enfants asthmatiques, sans symptôme respiratoire, fournissent généralement des valeurs plus basses qui sont révélatrices d'une obstruction bronchique. Le rapport CPUE/CV offre une corrélation satisfaisante avec notre classification clinique de malades asthmatiques à savoir que ceux qui présentent des symptômes sévères (Groupe III) donnent les valeurs les plus basses, tandis que les valeurs des autres cas se rapprochent de ceux du groupe de contrôle. Une valeur basse du rapport CPUE/CV peut être considérée comme un signe d'une obstruction bronchique. Le procédé est simple et rapide et offre un minimum d'inconvénient pour l'enfant.

Atmungsstudien bei Kindern. VI. Die zeitlich berechnete Vitalkapazität bei gesunden und symptomfreien Asthma-Kindern.

Es wurde die Relation zwischen der 1 Sekunden-Kapazität und Vitalkapazität, $V_{1\text{sec}}/V_{\text{VC}}$, an 17 gesunden, 7–12 Jahre alten Kindern und an 38 symptomfreien Asthma-Kindern im Alter von 6–14 Jahren bestimmt. Die Relation $V_{1\text{sec}}/V_{\text{VC}}$ ist unabhängig von der Körpergrösse. Der Mittelwert bei gesunden Kindern ist 0,869, was gut mit den bei Kindern und Erwachsenen gefundenen Werten anderer Autoren übereinstimmt. Die symptomfreien Asthma-Kinder ergeben niedrigere Werte als ein Zeichen von bronchialer Obstruktion. Die Relation $V_{1\text{sec}}/V_{\text{VC}}$ zeigt eine gute Korrelation mit unserer klinischen Bewertung von Asthma-Patienten, d. h. die schwierigen Fälle (Gruppe III) haben eindeutig niedrigere Werte, während die anderen Fälle sich den Werten der Kontrollgruppe nähern. Ein niedriger Wert der Relation $V_{1\text{sec}}/V_{\text{VC}}$ kann als Ausdruck der bronchialen Obstruktion angesehen werden. Die Durchführung ist einfach, braucht nur wenig Zeit und beeinträchtigt das Kind nur minimal.

Estudio de la respiración en la infancia. VI. La medida de la Capacidad Vital en la unidad de tiempo en el niño normal y en el niño asmático sin síntomas respiratorios.

La relación entre la capacidad vital en 1 segundo y la capacidad vital ($V_{1\text{sec}}/V_{\text{VC}}$) fué determinada en 17 niños sanos de 7 a 12 años de edad, y en 38 niños asmáticos sin síntomas de 6 a 14 años de edad. La relación $V_{1\text{sec}}/V_{\text{VC}}$ es independiente de la talla corporal, con un valor medio de 0,869 en los niños sanos, lo que está totalmente de acuerdo con los valores hallados por otros autores en niños y adultos. Los niños asmáticos, sin sintomatología, generalmente dan valores más bajos, como un signo de obstrucción bronquial. La razón $V_{1\text{sec}}/V_{\text{VC}}$ se muestra en correlación con nuestra clasificación clínica de los pacientes asmáticos, por ej.: aquellos clasificados como casos severos (Grupo III), tienen, significativamente, los valores más bajos, mientras que los otros dan cifras más próximas al grupo de control. La razón reducida $V_{1\text{sec}}/V_{\text{VC}}$ puede ser usada como expresión de la obstrucción bronquial. El procedimiento es sencillo, rápido y acarrea el mínimo de molestias al niño.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60, Sweden

On Inorganic Pyrophosphate Content of Human Blood Plasma

by J. HARRI

Using the method described by Flynn *et al.* (1) for the determination of inorganic pyrophosphate in biological material, Riih  *et al.* (2) obtained a positive reaction in human blood plasma, but were not convinced that there is inorganic pyrophosphate in the plasma. The production of a colour by a reaction between pyrophosphate and molybdate catalyzed by cysteine which forms the basis of the method is not, however, specific for pyrophosphate since organic phosphates may undergo hydrolysis under the conditions of the test and the orthophosphate formed may intensify the development of colour. The result is not, on the other hand, in agreement with the known fact that the difference between the total phosphorus content of the soluble fraction of the plasma and the phosphorus present as inorganic orthophosphate in the plasma (which latter as determined by the Fiske-Subbarow method does not include inorganic pyrophosphate) is only a few tenths of a milligram per 100 ml, which difference should thus represent both inorganic pyrophosphate and organic phosphates. In the present study a specific enzymatic method has been developed for the determination of inorganic pyrophos-

phate and has been applied to decide whether inorganic pyrophosphate is present in human blood plasma.

Method

The method is based on the determination of the activity of inorganic pyrophosphatase according to Kunitz *et al.* (3). The orthophosphate liberated has been analysed using the reagents employed in the Fiske-Subbarow method (4). The detailed description of this method will be published elsewhere. The oxalated or heparinized blood specimens were cooled in ice water immediately after collection and the plasma separated by centrifugation near 0°C. The specimens must not be hemolysed since red cells contain abundant inorganic pyrophosphatase which will very rapidly hydrolyze any inorganic pyrophosphate present. Since calcium ions inactivate inorganic pyrophosphatase, they must be removed from the plasma. Oxalate plasma can be employed directly (oxalate concentration about 0.3%). The plasma of heparinized blood can be decalcified by treating it with, for instance, Dowex 50 ion exchange resin in the sodium form.

The enzymatic hydrolysis of inorganic pyrophosphate to orthophosphate was made with a hexokinase-inorganic pyrophosphatase preparation, 10 mg of which were dissolved in 10 ml of 0.002 M veronal buffer solution. The activity of the pyrophosphatase solution is adjusted to be sufficient to hy-

hydrolyse the inorganic pyrophosphate assumed to be present in the specimen. Four ml of 0,1 M veronal buffer and 1,0 ml of 0,001 M $MgCl_2$ solution is added to all test tubes. Two ml of water is added to the blank tube, 2,0 ml of decalcified plasma to both plasma blank and actual plasma tubes, and 2,0 ml of standard solution containing 2,5 mg% P as pyrophosphate to the standard-tube. The test tubes are then placed in an incubator at 30°C. After the tubes have warmed to the incubator temperature, 1 ml of 0,02 M veronal buffer solution is added to the tubes containing water and plasma blanks and 1,0 ml of enzyme solution to the actual plasma and standard tubes. After the tubes have been incubated about 25 minutes, 2,0-ml aliquots are pipeted into 3,0 ml of 6 per cent trichloroacetic acid. The determination of orthophosphate in the supernatant fluid is carried out after centrifugation as follows:

To 2,0 ml of the centrifugate are added 0,5 ml of ammonium molybdate solution acidified with sulphuric acid, water to give 5,0 ml, and 0,2 ml of eikonogen solution, and the mixture is shaken vigorously. After 15 minutes the colour intensity is measured against the water blank with a Klett-Summerson photometer using the filter 66. The phosphorus content is obtained by subtracting from the reading of the test solution the reading of the plasma blank. The difference is directly proportional to the phosphate content which is evaluated as pyrophosphate-P by comparison with the pyrophosphate standard.

Results

1. Several normal plasma specimens from different persons were analysed for inorganic pyrophosphate. No increase was observed in the orthophosphate content following enzymatic hydrolysis in any of the plasma specimens as stated by the difference between actual plasma and blank tests.

The following tests were carried out to confirm this result.

2. Orthophosphate determinations carried out on plasma blanks before and after incubation showed that the amount of orthophosphate did not change during the incubation. This eliminates the possibility that any inorganic pyrophosphate present in the plasma becomes hydrolysed also in the plasma blank determination and is not therefore detected in the actual determination, which was made after incubation.

3. Recovery tests were performed by adding a known amount of sodium pyrophosphate to known volumes of oxalated blood. From some of the specimens the plasma was separated immediately, but some of the specimens were allowed to stand 4 hours at room temperature and some 4 hours at +4°C before the plasma was separated. The results obtained were compared with the pyrophosphate content computed from the hematocrit value of the plasma. The pyrophosphate content varied from 0,5 to 2,5 mg % of phosphorus. The recoveries in all three cases varied from 88 to 105 per cent. This variation may be ascribed to errors resulting from the complexity of the procedure. It is in any case obvious that no diffusion of inorganic pyrophosphate into the red blood cells had taken place under the conditions of the analysis, which might have been the reason why no inorganic pyrophosphate was found in the plasma specimens.

These results demonstrate clearly that normal human plasma contains no inorganic pyrophosphate and that there is no passage of inorganic pyrophosphate from the plasma into the red cells under the conditions of the test.

Acknowledgement

I am grateful to prof. C.-E. R  ih  , whose research group made the observation that led to the present study and who has kindly advised me during the work. I am

also indebted to prof. Olof Lindberg (Wenner-Gren Institutet, Stockholm) for placing the hexokinase-inorganic pyrophosphatase preparation at my disposal.

Summary

The author has developed a specific enzymatic method for the determination of inorganic pyrophosphate in the plasma. By this method it is found out that no inorganic pyrophosphate occurs in human blood plasma. The blood specimens were cooled in ice water immediately after collection and the plasma separated by centrifuging at 0  C. Recovery experiments showed that no losses of inorganic pyrophosphate from plasma into the red blood cells occurred under the conditions of the test.

Teneur de pyrophosphate inorganique dans le plasma sanguin chez l'homme.

L'auteur a mis au point une m  thode sp  cifique enzymatique pour la d  termination du pyrophosphate inorganique dans le plasma. On a trouv  ,    l'aide de cette m  thode, qu'il n'y a pas de pyrophosphate inorganique dans le plasma sanguin chez l'homme. Les sp  cimens sanguins ont   t   refroidis imm  diatement apr  s collection dans de l'eau glac  e et le plasma a   t   s  par   par centrifugation    0  C. Des exp  riences de r  cup  ration ont d  montr   qu'il n'y a pas eu de perte de pyrophosphate inorganique du plasma dans les globules sanguines pendant le test.

  ber den Gehalt an anorganischem Pyrophosphat im menschlichen Blutplasma.

Verfasser hat ein spezifisches Enzymverfahren zur Bestimmung des Gehalts an anorganischem Pyrophosphat im Plasma ausgearbeitet. Mit Hilfe dieses Verfahrens wurde nachgewiesen, dass anorganisches Pyrophosphat im menschlichen Blutplasma nicht vorhanden sei. Das zu untersuchende Blut wurde unmittelbar nach der Entnahme in eiskaltem Wasser gek  hlt und das Plasma bei 0  C abzentrifugiert. R  ckgewinnungsexperimente zeigten, dass keine Verluste von anorganischem Pyrophosphat vom Plasma in die roten Blutk  rperchen unter den angewandten Versuchsbedingungen erfolgten.

Contenido en pirofosfato inorg  nico del plasma humano.

El autor ha ideado un m  todo fermentativo espec  fico para la determinaci  n del pirofosfato inorg  nico del plasma. Mediante este m  todo se demostr   que el plasma sangu  neo humano carece de pirofosfato inorg  nico, las muestras de sangre se enfriaron en agua helada inmediatamente despu  s de ser recogidas, y el plasma se separ   por centrifugaci  n a 0  . Experimentalmente se demostr   la ausencia de p  rdidas de pirofosfato inorg  nico del plasma los hemat  es, en las condiciones en que se efectu   la prueba.

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Institute of Biochemistry
University of Helsinki
Helsinki
Finland

Staphylococci in a Children's Hospital

Studies on the effect of an antiseptic hand cream and the distribution of antigenic activity of strains isolated from different sites

by GUNNAR LAURELL

The importance of staphylococci in hospital infections is now being widely recognized, and numerous reports from many parts of the world have drawn attention to the recent increase in infections.

Reports of epidemics have come from such different units as paediatric, surgical, obstetric, gynaecologic, and internal medicine departments. Pathways of dissemination have been studied, but very little is still known about the mechanism by which transmission occurs. Several preventive measures have been tried but the results have been variable and at times negative, not least in the trials with antimicrobial agents.

During the last few years, factors determining the virulence of *Staph. pyogenes* have been studied closely. Among other things it has been demonstrated that strains isolated from pyogenic skin infections produce more diffusible toxins than those recovered from the upper respiratory tract of healthy carriers (1, 6, 14, 15, 17).

The present study was carried out at the paediatric department of the University Hospital in Uppsala from August

1956 to May 1957. Its aim was to test the prophylactic effect of a bactericidal cream, to compare *Staph. pyogenes* from different sites, and to analyse the contamination of the depots. The cream (Hibitane ICI) contains chlorhexidine as active substance and should be used for continuous hand disinfection, and can also be used for local application to the nares. According to some reports it diminished the carrier rate of *Staph. pyogenes* and reduced the incidence of hospital infection (3, 10, 11, 12, 13, 16).

Material and Methods

Sampling and Cultivation. Specimens were collected once a week from the nose and throat of the hospital staff and children of the two wards investigated. Ordinary throat and nasopharyngeal swabs were used. After sampling, the swabs were placed in agar slope tubes for immediate delivery to the laboratory. The specimens were inoculated on meat infusion agar with 10 per cent sheep's blood, phenolmannitol agar with 7.5 per cent sodium chloride according to Chapman, and ordinary broth with 6.5 per cent sodium chloride for enrichment. The plates were incubated aerobically at 37°C and read after 24 and 48 hours. The phenol-mannitol

plates were also read after a further 24 hours at room temperature. When no staphylococci were demonstrable on direct culture, secondary cultures were made from the broth on blood agar plates. Suspected colonies were coagulase-tested with the tube method. All coagulase-positive staphylococci were included in the analysis irrespective of pigmentation, being termed *Staph. pyogenes*.

Application of the Cream. Two creams were used, the English original preparation and one prepared by AB Pharmacia, Sweden. The active substance was the same in both preparations. The original English cream and the active substance were kindly supplied by AB Meda, Gothenburg. In one of the two wards investigated, that for infants, the tubes of cream were placed beside each washbasin so as to be easily accessible. The staff were instructed to use the preparation after handling each patient and also to smooth it into the skin around the nostrils once a day. A tube was also placed on the patient's table and the infant's hands and nostrils were treated after each handling. In the other ward, for older children, it was thought unwise to have the tubes of cream in the wards. They were kept in the service rooms at the washbasins and the staff were issued with their own tubes. Otherwise, the application of the cream was the same as for the infants.

Finger Test. The technique described by Murray & Calman (16) was used. The hands were washed with soap and water and dried on a clean towel. A sterile rubber finger-stall moistened on its inner surface with 0.5 ml broth was then placed on the index finger of the right hand. The stall was removed after 30 minutes and filled with 1 ml broth. One half millilitre was then pipetted off and mixed with 1.5 ml isotonic sodium chloride containing 25 per cent serum. After further dilution to 1:10, 1 ml of the mixture was spread on blood and phenol-mannitol plates.

Environment Tests. Blood agar plates were used throughout for these analyses, and sodium chloride broth for enrichment. Weighing machines and tables, various toys, wash-

basins, textiles, and the like were examined. Samples were taken with ordinary throat swabs dipped in broth. Air analysis was performed with a Bourdillon slit sampler. Textiles were tested according to Blowers & Wallace (2) by passing a blood agar plate with the agar surface facing the fabric to be tested so that fine particles swirled up onto the medium.

Antigenic Activity and Phage Typing

Fibrinolysin. Fibrinolysin production was determined with Christie & Wilson's (4) technique, with agar plates containing fibrin-agar. The results were assessed as positive or negative; no quantitative analysis was made.

Haemolysin. The production of alpha, beta, and delta toxin was determined with the antitoxin strip method described by Elek & Levy (6). The strip was saturated with Burroughs and Wellcome's commercial serum prepared from the strain Wood 46. Quantitative haemolysin determinations were carried out according to Anderson (1).

Total Diffusible Antigens. A modification of the method described by Anderson (1) was used. The paper strip saturated with antitoxin was replaced by a plate with a 8 by 38 mm basin. The basin was filled with agar containing 500 units antitoxin per millilitre. The medium on the rest of the plate was brain heart infusion (Difco) with a final agar concentration of 1.5 per cent. The strains to be studied were inoculated as streaks at right angles to the basin. After 48 hours incubation at 37°C in 30 per cent CO₂ atmosphere, and 24 hours in a refrigerator, the number of precipitation lines were counted.

Phage Typing. Selected strains isolated from the upper respiratory tract and from finger tests were phage typed. The typing was done by Gösta Wallmark, M.D., at Statens Bakteriologiska Laboratorium, Stockholm.

Results

Hospital Staff. The effect of Hibitane on the incidence of *Staph. pyogenes* in the

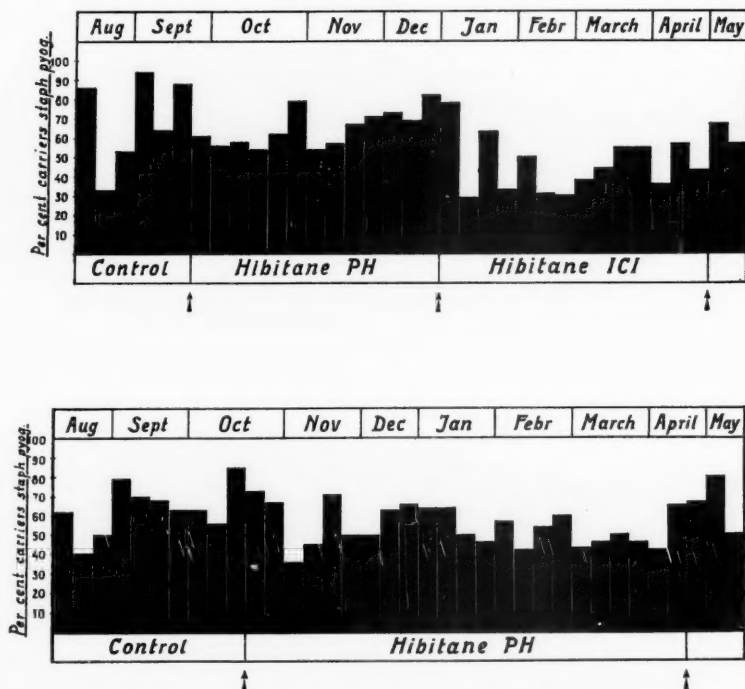


Fig. 1. Incidence of *Staph. pyogenes* in the upper respiratory tract of the nursing staff. Hibitane PH marks the period when the cream manufactured here was under test, and Hibitane ICI indicates the period during which the original English cream was in use. The upper part of the figure refers to the staff of Ward No. 11 for older children, and the lower part to that of Ward No. 12 for infants.

upper respiratory tract is illustrated in Fig. 1. Only those members of the staff examined three times (in whom the period of observation was at least three weeks) are included in the figure. In the two wards tested, No. 12 for infants and No. 11 for older children, this criterion left 54 and 48 individuals respectively for analysis. As will be seen in the figure, no decrease whatever was noted in ward No. 12, while a possible slight effect was noted in No. 11. Here the incidence of *Staph. pyogenes* decreased from the 60 to 80 per cent recorded before using the English cream to

between 30 and 50 per cent, higher values being noted only occasionally.

Some points of interest emerged, not directly connected with the application of the cream. Owing to the fairly long period of observation, some members of the staff were sampled several times. Among 35 nurses (observed for 10 weeks and sampled at least 10 times) two types of carrier could be distinguished. In one group of 19 persons, *Staph. pyogenes* was fairly consistently isolated and the incidence of positive cultures was at least 70 per cent, ranging up to 90 per cent or more in 6 of them. In

a smaller group of 4 nurses the opposite applied positive cultures being noted in at most 10 per cent. In further three persons, no *Staph. pyogenes* was isolated at any time. The remaining nurses were more of the transient carrier type, positive cultures alternating with negative.

No noteworthy decrease in the incidence of *Staph. pyogenes* was noted in the upper respiratory tract of the infants and children of the two wards. The incidence varied widely between 50 and 90 per cent, but was neither strikingly high nor strikingly low for any particular length of time.

Finger Test. It was not possible to keep a continuous watch on the effect of the cream as a hand disinfectant, but the tests were concentrated to March and April 1957. Altogether 58 subjects were examined with 257 tests. Coagulase-positive staphylococci were isolated from no less than 44 of these cases. Detailed analysis showed a not infrequent decrease in the amount of contamination, but it was not

possible wholly to eliminate the staphylococci from the skin.

Environment Tests. The results are presented in Table 1. As will be seen there, the environment was heavily contaminated with *Staph. pyogenes* isolated from the air and all the nursing utensils examined. Had the tests been extended to include other objects, staphylococci would almost certainly have been recovered from even more sites. It was of special interest to note that staphylococci occurred extensively on "clean" textiles.

Antigenic Activity and Phage Typing

Haemolysin and Staphylokinase Assay.

The material consisted of strains isolated from the throat, nose, and fingers of 45 persons. In 31 cases the bacteria were isolated from both the upper respiratory tract and the finger, in 8 only from the respiratory tract, and in 6 only from the finger. Altogether 80 respiratory tract and 45 finger strains were studied. The strains

TABLE 1. *Environment Tests.*

Object	Number of tests	Tests containing <i>Staph. pyogenes</i>	
		No.	%
Cloth toys	20	13	65
Wooden toys	20	12	60
Plastic toys	20	6	30
Weighing machines	20	15	75
Weighing tables	20	9	45
Washbasins	20	3	15
Used blankets	14	4	28
Used sheets	10	8	80
Clean blankets	20	8	40
Clean pillows	20	14	70
Clean mattresses	18	8	44
Air Sampler ¹	10	6	60

¹ Air analyses were performed with a Bourdillon slit sampler, 400 to 500 litres air being examined on each occasion.

TABLE 2.

	No. of strains tested	Per cent positive			
		α -toxin	δ -toxin	β -toxin	Stafylokinase
Nose and throat	80	91.2	97.5	12.5	96.2
Finger	46	46.6	91.3	0	48.8

ability to elaborate alpha, beta, and delta haemolysin and staphylokinase will be found in Table 2. As is shown clearly in the table, the respiratory tract strains produced more alpha haemolysin (91.2 per cent) than the finger strains (46.6 per cent). The former also produced delta haemolysin in about the same frequency as the

TABLE 3. *Number of Antigen—Antibody Precipitation Lines Produced by Coagulase-Positive Staphylococci Isolated from Nose—Throat—Fingers.*

	Number of strains	Per cent of strains 0-3	Producing the number 4-7	indicated of lines 8-11
Nose and throat	80	10.0	26.2	63.8
Finger	46	51.1	17.8	31.1

latter, the figures for the two being 97.5 and 91.3 per cent. Beta haemolysin was elaborated only by the respiratory tract strains, 12.5 per cent. The figures for staphylokinase were 96.2 per cent for the respiratory tract strains, and 48.8 per cent for the finger strains.

Diffusible Antigen Production. The ability of the strains to produce diffusible antigens is given in Table 3. As will be seen in the table, the respiratory tract strains on the whole gave rise to appreciably more precipitation lines than the finger strains. Among the nose and throat strains, 63.8 per cent. formed 8 or more lines. The corresponding figure for the finger strains was 31.1 per cent. The difference is most striking when comparing the incidence of strains forming 0-3 lines. Among the respiratory tract strains this applied in 10.0 per cent, and among the finger strains in 51.1 per cent. There was difficulty at times in exactly determining the number of precipitation lines, since they were in some measure diffuse and difficult to distinguish. The number of sharp lines varied as a rule between 3 and 6. No attempt has yet been made to identify the toxin represented by a certain line.

Phage Typing. The results of this ex-

TABLE 4. *Phage Patterns among 125 Strains of Staph. Pyogenes Isolated from Nose, Throat, and Fingers.*

Phage group	Phage pattern	Number of strains	
		Nose + throat	Finger
I	80/KS 6	2	1
	52/52 A/80/KS 6		2
	Total	2	3
II	3 A	8	2
	3 B/3 c/55/71	5	
	3 B/3 c/55	3	
	55	1	
	Total	17	2
III	61/47/53 +	2	
	47/54/75/77/819/1034	5	3
	47/53/75	2	
	75/77/1034 +	3	2
	47/54/1034/166/155	2	
	819/1034	2	
	9 different patterns	6	4
	Total	22	9
I + III	79/80/75/77/1034	3	1
	2 different patterns	2	1
	Total	5	2
	Non-typable	34	29
	Grand total	80	45

amination will be found in Table 4. As will be seen there, 57.5 per cent of the respiratory tract strains reacted with phages, while this occurred in only 35.5 per cent of the finger strains. Classification into phage groups showed 21.3 per cent of the nose and throat strains to belong to Group II, and 27.5 per cent to Group III. The corresponding figures for the finger strains were 4.4 and 20.0 per cent. No particular phage type predominated.

Comparison of the Results of Different Tests. In view of the results obtained on comparing staphylococci from different infections and from carriers, a corresponding analysis was thought to be of interest here. Those strains examined as to phage type,

production of diffusible antigens, haemolysin, and staphylokinase were studied. It was found that the greater number of typable strains from the upper respiratory tract produced larger amounts of diffusible antigens, and that only 3 of 46 strains formed less than 3 precipitation lines. Non-typable strains also showed high activity, but 5 of 34 formed less than 3 precipitation lines. Among the finger strains, 1 of 16 typable strains formed less than 3 precipitation lines, and among the non-typable 22 of 29. This tendency to lower activity among the finger strains, particularly the non-typable, was also noted in the other tests. All typable respiratory tract strains produced staphylokinase and only two of the non-typable strains lacked this faculty. Among the finger strains, 2 of the typable and 20 of the non-typable strains failed to produce staphylokinase. Alpha lysin was not produced by 1 of the typable and 5 of the non-typable strains from the nose and throat. The corresponding figures for the finger strains were 2 and 22. No

great difference as regards delta lysin emerged between different types of strains, as is seen in Table 2. Some typical cases are compiled in Table 5 by way of illustration.

In Table 5 it will be seen that in Case 1 typable staphylococci were isolated from the nose and non-typable from the throat and finger. The two respiratory tract strains showed on the whole the same antigenic activity, while the finger strain produced only coagulase and delta lysin and gave rise to one precipitation line. Case 2 showed largely similar features but in this instance both respiratory tract strains were typable. In Case 3 all the strains were typable and belonged to the same type. The two respiratory tract strains and the finger strain showed on the whole the same antigenic activity, although the finger strain produced somewhat less alpha lysin. Case 4 illustrates a less usual feature in that the finger strain was typable but not the respiratory tract strains. It is of interest to note that the finger strain appeared to

TABLE 5.

Case	Isolated from	Phage pattern	Coagulase	Staphylokinase	Production of haemolysin			Titre alpha haemolysin	Number precipitation lines
					Alpha	Beta	Delta		
1	Nose	79/80/53/75/77/1034	+	+	+	-	+	1/8	10
	Throat	"	+	+	+	-	+	1/16	9
	Finger	N.T.	+	-	-	-	+	-	1
2	Nose	1034	+	+	+	-	+	1/32	10
	Throat	3 B/3 C/55	+	+	+	-	+	1/16	10
	Finger	N.T.	+	-	-	-	+	-	2
3	Nose	80 KS 6	+	+	+	-	+	1/8	7
	Throat	"	+	+	+	-	+	1/16	7
	Finger	"	+	+	+	-	+	1/4	7
4	Nose	N.T.	+	+	+	-	+	1/32	10
	Throat	N.T.	+	+	+	-	+	1/16	10
	Finger	3 A	+	+	+	-	+	1/32	5

show lower antigenic activity, although this was demonstrable solely by comparison of the number of precipitation lines formed.

Discussion

The present study was directed to ascertaining the effect of an antiseptic hand cream, Hibitane, in which the active substance is chlorhexidine. Its effect upon the incidence of staphylococci in the upper respiratory tract was non-existent in infants and children, and negligible in the hospital staff. In one of the two wards investigated, that for infants, no decrease was noted. In the ward for older children the incidence among the staff was between 30 and 50 per cent while the English cream was in use, having formerly ranged from 60 to 80 per cent. The reason for this possible decrease may have been that the danger of exposure is less in a ward treating older children than in one caring for infants. The decrease, if it was in fact such, appeared to consist in a longer period of freedom from staphylococci while the English cream was in use among non-carrier members of the staff. As a hand disinfectant, the preparation also appeared to be of slight value. The incidence of staphylococci was in fact higher than is usually recorded in investigations of this type. However, the cream was probably not entirely without effect. *In vitro* experiments showed it to be effective against staphylococci, and detailed analyses showed a frequent decrease in the amount of staphylococci isolated. But it was usually not possible wholly to eradicate staphylococci from the skin, and it even happened while the cream was in use that staphylococci were found upon the skin of persons

in whom they had formerly been absent. The poor effect may possibly be accounted for by the fact that the "finger-stall method" brings out the so-called residential flora from the deeper levels of the skin upon which a bactericidal cream cannot exert sufficient effect. Analysis of the environment showed staphylococci to be present everywhere, being recovered from the air, weighing machines and tables, toys washbasins, and fabrics. It is of interest to note that even "clean" textiles were infected. The present study agrees fully with the results of numerous recent investigations as regards the aspects mentioned above, carrier frequency and the heavy contamination of the environment.

Closer analysis of a selection of coagulase-positive strains from the upper respiratory tract and finger tests gave several interesting results. Alpha haemolysin was produced by 91.2 per cent of the nose and throat strains, while this applied to only 46.6 per cent of the finger strains. The corresponding figures for staphylokinase production were 96.2 and 48.8 per cent. None of the finger strains elaborated beta haemolysin. The strains from the upper respiratory tract showed a larger production of diffusible antigens and were in greater measure phage typable. Of the respiratory tract strains 57.5 per cent reacted with phages, and of the finger strains 35.5 per cent. No single phage type predominated. Comparison of typability and antigenic activity showed the typable strains from the respiratory tract and finger to produce more haemolysins, staphylokinase, and diffusible antigens than the non-typable strains. The non-typable finger strains in particular showed low activity. This is a feature of interest, since

several authors report a close correlation between the antigenic activity and pathogenicity of staphylococci. This correlation has been demonstrated in clinical series by Schwabacher *et al.* (17), Anderson (1), and Hinton (8). Howard (9) found a similar correlation as regards pathogenicity for mice. The results arrived at in the present study suggest that only a minor number of the coagulase-positive staphylococci from the hands were pathogenic. The series is too small to permit of any definite conclusions and it should also be borne in mind that the results of these *in vitro* experiments and the pathogenicity of the bacteria are not necessarily directly correlated (5). In order to arrive at more conclusive results, study should include animal experiments (18) and extended an-

tigenic tests. The original derivation of the finger strains cannot be determined. The phage typable staphylococci in all probability originated in the respiratory tract, but the non-typable strains may have had several sources. They may possibly have derived from the respiratory tract and on adapting themselves to the new environment, the skin, lost the ability to produce certain toxins and their phage typability. Equally, they may have been mutants, and the possibility that their source may have been other than the respiratory tract cannot be ruled out. It would be of interest in this connexion to distinguish the characteristics of the staphylococci isolated from dust, air, fabrics, and the like. Studies to this end are in progress.

Summary

The incidence of *Staph. pyogenes* in the infants and children, hospital staff, and environment of two wards was investigated during a period of 10 months. In order to decrease the carrier frequency and the danger of contact infection an antiseptic hand cream, Hibitane, was tested. The effect on the respiratory tract carrier rate was non-existent among the infants and children, and very slight among the staff. Hand contamination with *Staph. pyogenes* was diminished but not eliminated. Certain toxigenic properties of 80 strains isolated from the upper respiratory tract and the hands were also studied. Strains recovered from the respiratory tract were shown to produce more diffusible antigens, alpha and beta haemolysin, and staphylokinase than those isolated from the hands. They were also in greater measure phage typable.

Staphylocoques dans un hôpital pour enfants. Etudes sur l'effet d'une crème antiseptique pour les mains et la distribution de l'activité antigénique de souches isolées de différents endroits.

L'indice de staphylocoques pyogènes a été examiné pendant une période de 10 mois chez les nourrissons et les enfants, le personnel de l'hôpital et aux environs de deux salles. Afin de réduire la fréquence des porteurs de bacilles et le danger d'une infection par contact, on a essayé une crème antiseptique pour les mains, l'Hibitane. L'effet par les voies respiratoires sur le taux de porteurs de bacilles était nonexistant parmi les nourrissons et les enfants, et très faible parmi le personnel. La contamination par les mains avec les staphylocoques pyogènes était diminuée mais non pas éliminée. On a également examiné certaines propriétés toxigéniques de 80 souches isolées de la voie respiratoire supérieure et des mains. Les souches récupérées des voies respiratoires semblaient produire

davantage d'antigènes diffusibles, l'hémolysine alpha et bêta, et la staphylokinase, que celles isolées des mains. Elles s'adaptent également dans une plus grande mesure à l'application des bactériophages.

Staphylokokken in einer Kinderklinik. Untersuchungen über die Wirkung eines antiseptischen Handcremes und die Verbreitung der antigenen Aktivität der Bakterienarten, welche aus den verschiedenen Lagen isoliert werden.

Der Einfluss von Staph. Pyogenes bei Säuglingen und Kindern, beim Klinikstab und in der Umgebung von 2 Krankenhausabteilungen wurde während einer Periode von 10 Monaten erforscht. Bezüglich der Abnahme wurden die Keimträgerhäufigkeit, die Gefahr der Kontakt-Infektion und der antiseptische Hancreme, Hibitane, geprüft. Die Wirkung auf den Respirations-Tractus bei dem Keimträger-Anteil war bei den Säuglingen und Kindern nicht vorhanden und nur sehr unbedeutend beim Krankenhauspersonal. Händeverunreinigung mit Staph. Pyogenes war vermindert, aber nicht völlig verschwunden. Bestimmte toxische Eigenschaften von 80 Abstrichen, die aus dem oberen Respirations-Traktus und den Händen abgenommen waren, wurden auch studiert. An Abstrichen aus dem Respirations-Traktus wurde erwiesen, dass sie mehr zerstreute Antigene, alpha- und beta-Hämolysine und Staphylokinase produzieren als jene, welche von den Händen abgenommen worden sind. Sie waren auch in grösserem Masse ausgeprägter.

Estafilococos en un hospital de niños. Estudio sobre la acción de una crema antiséptica para las manos y la distribución de la actividad antigénica de cepas aisladas de diferentes lugares.

Durante un período de diez meses se investigó la incidencia de estafilococos piógeno en los niños, personal del hospital, y medio ambiente de dos pabellones. Se probó una crema antiséptica para las manos, Hibitane, a fin de disminuir la frecuencia de portadores y el peligro de la infección por contacto. La acción sobre las vías respiratorias de los portadores fue nula entre los niños y muy escasa entre el personal. La contaminación manual con estafilococo piógenos disminuyó pero no se eliminó. También se estudiaron diversas propiedades toxicogénicas de ochenta cepas aisladas de las vías respiratorias superiores y de las manos. Las cepas obtenidas de las vías respiratorias se demostró que elaboraban más antígenos difusibles, hemolisinas alfa y beta, y estafiloquinasa que las aisladas de las manos.

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Institute of Bacteriology
University of Upsala
Upsala
Sweden

From the Pediatric Clinic of the State University at Ghent, Belgium
(Director: Prof. C. Hooft, M.D.)

Aminoaciduria in the Course of Lipoid Nephrosis in Children. The Influence of ACTH

by C. HOOFT and J. HERPOL

The majority of data hitherto found in the literature on the urinary amino-acid excretion in nephrosis have been obtained by paper chromatography. A few findings were also published which had been obtained by microbiological methods (30, 33, 35). Although the cases discussed in this literature are chiefly instances of genuine lipoid nephrosis in children, yet the series published are not always homogeneous in this respect, and the results obtained by the various investigators remain relatively diverse.

There is first a group of authors who found no significant increase in the urinary excretion of free amino-acids in association with nephrosis (2, 4, 32, 36). Plückthun *et al.* and Berger made the same observation but pointed out that in the case of oliguria urinary amino-acid concentrations can be very high although 24-hour excretion is normal.

A second group of investigators observed unmistakable hyperaminoaciduria in nephrotic patients, but only under special conditions, viz.

(a) during treatment with a high-protein diet (5, 23, 37, 38);

(b) during administration of protein hydrolysates, either orally or intravenously (7, 28, 34);

(c) during treatment with ACTH (33).

A very important investigation was finally reported by Woolf & McC.Giles¹ in 1956; they found such a hyperaminoaciduria in as many as 25 out of 28 children with lipoid nephrosis. It was pointed out that the 3 cases with normal aminoaciduria showed very slight clinical signs at the time of the examination. Otherwise the cases of hyperaminoaciduria observed can be divided into two groups according to the type (or pattern).

The *first type*, which the authors call *H-pattern* and consider prognostically favourable, is characterized by the presence of large quantities of compounds no longer containing α -amino nitrogen (i.e. *ethanolamine*, *β -amino-isobutyric acid*, *taurine*), and of somewhat less large quantities of the following α -amino-acids: *tyrosine*, *leucine* and *valine*. The *second type* is charac-

¹ A few data are also contained in a paper by McC.Giles *et al.* (1957); however, this concerns very special cases of nephrosis, which occurred in several infants in the same family.

terized by the predominance of a group of amino-acids, which as a rule may be found in considerable quantities in the blood, but which are hardly represented in the normal urine. These are chiefly *proline*, *leucine* and *isoleucine*, *valine* and *alanine*. This type is described as *R-pattern* and its prognosis is regarded as considerably less favourable.

Apart from Woolf & McC.Giles, a few other authors have mentioned unmistakable hyperaminoaciduria in cases of nephrosis, without giving identical descriptions (11, 14, 25, 35). Special mention should be made of the 4 cases of lipid nephrosis described by Tegelaers & Tiddens (1955), Tiddens (1957), Stanbury & Macaulay (1957) and Hooft & Vermassen (1958), in which the development of tubular renal insufficiency gave rise to a syndrome of de Toni-Debré-Fanconi: we regard these cases as an expression of a very special type of lipid nephrosis. These 4 patients showed a hyperaminoaciduria closely related to the *R-pattern* described by Woolf & McC.Giles.

Personal Observations

During a three-year period (from January 1955 to December 1957), we investigated the amino-acid level of the urine (and incidentally that of the blood also) in 22 patients with lipid nephrosis. During this period, ACTH therapy was systematically given according to the principles recently described by one of us (19, 20). Details re-

garding this therapy can be found in these publications, which also include a brief clinical description of the various possible developments.

These patients were aged from 12 months to 13 years at the beginning of our observations. Sex distribution was extremely unequal, in that only 4 of the 22 subjects under investigation were female.

Methods

With the exception of the two youngest patients, who were still incontinent, 24-hour urine collections were always used. Samples were stored at 4°C, after addition of a few crystals of thymol. If there was marked proteinuria on boiling, protein was precipitated with the aid of trichloroacetic acid at low temperature—a technique also used by Woolf & McC.Giles. In the other cases the urine was simply filtered and defaecated.

Fasting venous blood was invariably used for determination of the blood amino-acid level. The serum was extracted with acetone as suggested by Giddey (1953). The same method was used for the transudates which occasionally were also examined.

Identification and semi-quantitative estimation of the free amino-acids¹ present in these biological fluids were accomplished with the aid of the classic method of bi-dimensional paper chromatography (8). We used the ascending variant, with water-saturated-phenol in the first direction, and the ternary mixture butanol-glacial acetic acid-water in the second.

For the urinary chromatograms, 25–50 μ l was used, according to the child's age and the urinary output of the current 24 hours. For the remaining determinations we used a quantity of acetone extract corresponding

¹ Like many authors who have used this technique, we have been able to demonstrate repeatedly Dent's "nephrosis peptid" (1948). This compound—which occupies a very characteristic position on the chromatogram and which disappears following acid hydrolysis—was observed in 30 samples of urine, obtained from 10 patients. Its presence is quite inconstant, even in one given case, and it is completely independent of the amino-acid excretion. We have always seen this peptid in association with albuminuria, although no correlation with the degree of this albuminuria was ever established. Investigations into this compound have not been continued, and we are therefore unable to participate in the discussions of this subject found in the literature.

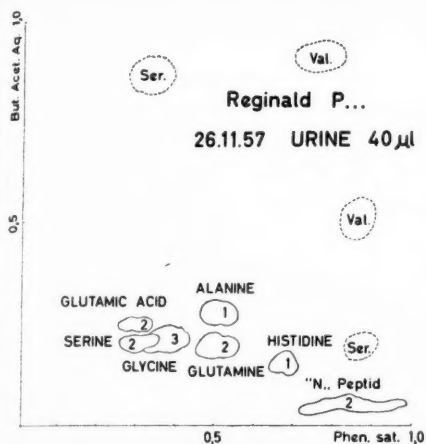


Fig. 1. Normal aminoaciduria in a case of lipid nephrosis. In every chromatogram shown here, the figures in the outlined spots correspond to the semi-quantitative estimation. (For *proline* and *hydroxyproline* a quotation from Y + to Y + + is used.) The dotted outlines marked *Ser.* and *Val.* show the position of markers run simultaneously on the same sheet in both directions as internal standards.

with 50 μ l of the original liquid. Further technical details have been discussed elsewhere and will be subsequently published (15).

Results

A total of 83 samples of urine were examined, obtained from 22 patients with lipid nephrosis. The amino-acid level of the blood was studied in only 11 patients, with a total of 22 blood samples. The investigation was chiefly concentrated on the 10 cases of nephrosis included in Table 1. In these cases, at least one complete episode of the affection was followed closely, either until complete clinical and serological remission (8 patients) or until a fatal issue (2 patients). No difference was made between initial stages of lipid nephrosis or relapses. The remaining patients were examined only occasionally, during variable stages of the clinical course.

Confining ourselves to the 58 urine samples obtained from the 10 patients in Table 1, overall results can be stated as follows:

1. Normal amino-aciduria was found in 31 urine samples (Fig. 1), although values were admittedly at the high limit of normal in 12. It is therefore possible that in a few instances a more sensitive quantitative method might have revealed a slight but unmistakable hyperaminoaciduria.

2. The remaining 27 samples were characterized by manifest hyperaminoaciduria. Three types were distinguishable, as follows:—

(a) A very marked hyperaminoaciduria, found in 16 samples, which contained considerable quantities particularly of neutral amino-acids with a long carbon-chain (α -aminobutyric acid, *valine*, *leucine* and *isoleucine*) and of aromatic amino-acids (*tyrosine*, *phenylalanine* and *proline*) (Fig. 2). In normal urine, these compounds are virtually always below the demonstrable concentration, whereas they are constantly found in the blood, both in normal cases and in nephrosis. It is beyond doubt that this type corresponds with the R-pattern described by Woolf & McC.Giles (1956).

(b) Three samples—all obtained from patient Alex L...—were characterized by a marked hyperaminoaciduria in which the following compounds predominated: *cystine*, *methionine*, *taurine*, *aspartic acid* and *asparagine*, and also β -amino-isobutyric acid (Fig. 3). This pathological excretion is reminiscent of the H-pattern described by Woolf & McC.Giles, but it shows an even more marked similarity to the hyperaminoaciduria seen in certain hepatic affections not associated with nephrosis.

TABLE 1. *Summary of clinical, serological, urinary, therapeutic and chromatographic data in 10 patients.*

Hy.ac. = Hyperaminoaciduria.

Case	Time and age at onset of the disease	Date of the investigations	Aminoaciduria	Therapy and any inter-current disease	Proteinuria g/100	Total Protein g %	Albumin g %	Total Lipid g %	Degree of oedema and transudates
1. Ghislain de B... †	June 49, 4 yrs	1955-1957	9 specimens with hy.ac. + + + (R-pattern)	See ref. 21	—	—	—	—	—
2. Eric D... †	June 56, 2 yrs	20.8.56 28.8.56	Hy.ac. + (R-pattern & N-peptid) Hy.ac. + (R-pattern)	— ACTH (8th day)	14 trace	4 3.9	0.6 0.6	2.9 2.6	+ + + + +
3. Armand de T...	End of 56, 5 ½ yrs	12.1.57 19.1.57 31.1.57 4.3.57 11.5.57	Hy.ac. + + (R-pattern) Hy.ac. + + (R-pattern) Hy.ac. + + (R-pattern) Hy.ac. + + (R-pattern) Hy.ac. + (R-pattern & N-peptid)	— Blood transfus. ACTH (1st day) ACTH (3rd day) Corteben (9th day after ACTH) ACTH (1st day)	14 8 16 14 3.5	4.1 — 4.3 3.5 5.8	0.5 — 1.0 0.9 1.6	3.1 — 1.8 3.9 1.9	+ + + + + + + + + + + + + +
		17.7.57 3.12.57	Normal Normal	—	trace trace	7.0 7.9	4.0 5.0	0.6 0.9	— —
4. Wim de W...	Sept. 54, 2 yrs	12.1.55 10.2.55 12.3.55 12.4.55 20.5.55	Normal ^a Normal ^a Normal ^a Normal Normal	— Chicken pox — ACTH (4th day) Corteben (9th day after ACTH)	6 trace trace 1 trace	4.6 5.8 7 5.5 6.1	1.1 2.2 3.9 1.7 3.8	1.9 0.8 0.5 1.4 0.6	+ + — — + —
		9.8.55	Normal	—	—	6.3	3.6	0.7	—
5. Alex L...	Early 53, 3 yrs	12.1.55 10.2.55 12.3.55	Normal ^a (N-peptid) Hy.ac. + (3rd type & N-peptid) Normal ^a (N-peptid)	— Chicken pox Corteben (10th day after ACTH) Corteben	3.5 8 3 15	3.6 4.3 4.6 3.9	0.8 0.9 1.1 1.2	3.1 3.0 2.5 1.8	+ + + + + + + + +
		29.3.55	Hy.ac. + (H-pattern?)	Early hepatitis	—	—	—	—	—
		12.4.55 20.5.55 24.12.56 28.12.56 5.4.57	Hy.ac. + (H-pattern?) Hy.ac. + (H-pattern?) Normal ^a Normal Hy.ac. + (3rd type)	Hepatitis End of hepatitis ACTH (3rd day) — ACTH (5th day)	3 trace — 2 11	4.0 5.2 6.7 7.0 7.0	1.2 1.5 2.3 2.7 3.5	1.5 1.1 0.7 0.8 0.7	— — — — —

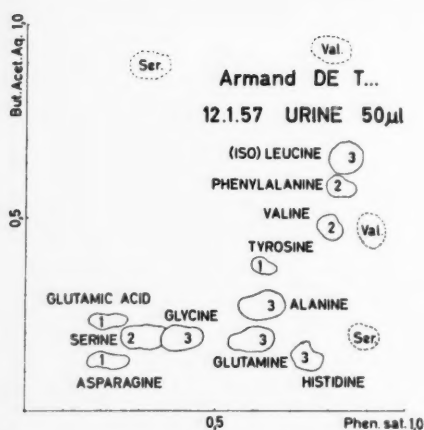


Fig. 2. Hyperaminoaciduria of the R-pattern in a nephrotic child.

(c) The remaining 8 samples of urine constitute a much less homogeneous group: the individual amino-acids mentioned under (a) and (b) are relatively often encountered but never in a characteristic association which predominated in the chromatogram. Quantitatively, this hyperaminoaciduria is very inconstant, being chiefly characterized by the abnormally large number and the unusual intensity of the spots which correspond with common amino-acids (Fig. 4). This third type therefore is not identifiable either with the R-pattern or with the H-pattern described by Woolf & McC.Giles.

Table 1 also shows that in the untreated cases of lipid nephrosis either a normal aminoaciduria (7 patients) or a hyperaminoaciduria of the R-pattern (3 patients) was found. The other two types of increased aminoaciduria were seen exclusively during the further course of nephrosis; treatment instituted and possibly intercurrent diseases must certainly be taken into consideration in this respect.

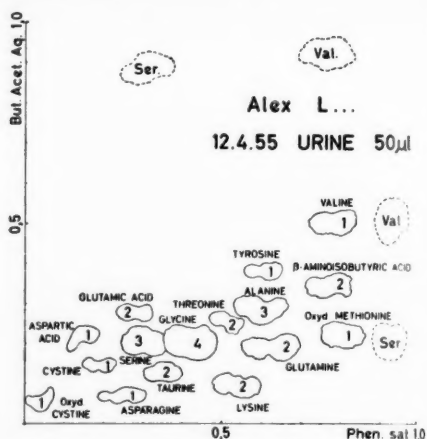


Fig. 3. Hyperaminoaciduria related to the H-pattern in a nephrotic child, also suffering from viral hepatitis.

Taking the clinical course into account, the results obtained can be presented as follows:

1. The 16 urine samples showing the R-pattern were obtained from 3 patients. One of these (Ghislain de B...) was described by Hooft & Vermassen (1958) as developing the complete clinical picture known as the de Toni-Debré-Fanconi syndrome. In this case there was a hyperaminoaciduria showing the R-pattern, which was found continually from the first paper-chromatographic determination until recent death. The exact time at which the hyperaminoaciduria first occurred could therefore not be established with certainty. Referring to the investigations made by Stanbury & Macaulay (1957) in an identical case, we presume that the hyperaminoaciduria occurred in this case only after considerable time; its appearance may have coincided with the occurrence of the renal glucosuria.

The remaining 2 patients, characterized by the R-pattern (Eric D... and Armand de T...), represent in our opinion a special type of lipid nephrosis, which will be discussed in detail in a subsequent publication. In connection with the clinical course in these

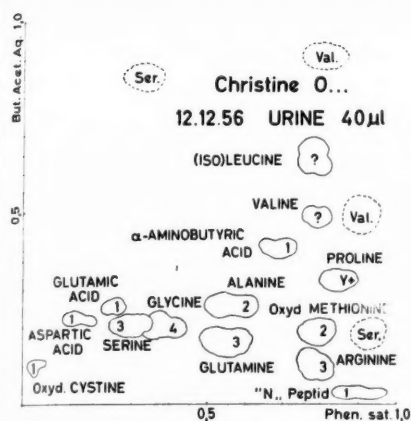


Fig. 4. Hyperaminoaciduria of a third type, associated with the ACTH therapy of lipid nephrosis.

cases, the following points can be mentioned here:

(a) These cases differ from the patient Ghislain de B... and the analogous patients described by Tegelaers & Tiddens (1955), Tiddens (1957), and Stanbury & Macaulay (1957), in the very fact that the hyperaminoaciduria was detected within the first weeks of illness.

(b) The development of clinical and serological signs following institution of an ACTH course at the dosage of 75–100 mg daily for 10 days, clearly deviated from the usual clinical course seen in other cases, in which ACTH is started shortly after the onset of symptoms characteristic of lipid nephrosis (18). In these two patients the diuresis remained very low during ACTH therapy, which also hardly influenced oedema, proteinuria and the serological picture.

(c) In the case of patient Armand de T... there was also renal glucosuria and decreased tubular phosphate reabsorption in addition to hyperaminoaciduria. The outcome after prolonged ACTH therapy ultimately took a favourable course, and all anomalous tubular renal functions subsequently returned to normal. The second patient, Eric D..., died

shortly after institution of therapy from peritonitis caused by *Escherichia coli*; the hyperaminoaciduria remained uninfluenced.

2. As has been pointed out, the 3 urine samples most closely related to the H-pattern of Woolf & McC. Giles (1956) were all obtained from patient Alex L... During the period of their collection this patient developed clinically manifest infectious hepatitis (virus hepatitis); this affection as such may induce the same kind of hyperaminoaciduria (4, 10, 22, 42). ACTH treatment was discontinued in this case after the diagnosis of hepatitis was made, and subsequently the cure of the hepatic condition was associated with a spontaneous remission of the lipid nephrosis; the aminoaciduria also showed normalization.

3. The remaining 8 samples with hyperaminoaciduria, which were regarded as a third type, were all collected after institution of ACTH-therapy (in 4 patients): in the active stage prior to treatment the amino-acid level of the urine was always normal. In the case of patients Christine O... and Gerard T..., the occurrence of hyperaminoaciduria exactly coincided with ACTH administration; in patient Paul van S... the increase in amino-acid excretion was also observed during a few days following discontinuation of ACTH therapy. In the case of the above-mentioned patient Alex L..., hyperaminoaciduria of this third type was also seen when ACTH treatment was discontinued in view of intercurrent chicken pox. Complete clinical and serological remission occurred in all patients. The aminoaciduria was invariably normalized in this event. The apparent correlation between transient hyperaminoaciduria in these 4 nephrotic patients and the administration of ACTH will be subsequently discussed in detail.

4. The 31 urine samples showing a normal amino-acid level were obtained from three groups of patients, viz.:

(a) Sixteen samples from the above-mentioned patients who showed transient hyperaminoaciduria, either of the R-pattern (1 case) or of the 2nd and 3rd type (4 cases).

(b) The remaining 15 samples were obtained from 3 patients in whom no hyperaminoaciduria was seen even during ACTH administration or in the course of an intercurrent infectious disease. Since these nephrotic patients were carefully followed from the onset of symptoms (Reginald P... and Daniel P...) or from the onset of relapse (Wim de W...) until complete clinical and serological remission, it is considered unlikely that increased amino-acid excretion ever occurred. Patient Daniel P... can be considered a case of acute nephrosis (Hooft & Vandenberghe, 1955), while the other two showed the chronic recurrent type of nephrosis.

A discussion of the results not included in Table 1 can be brief. They pertain to 25 urine samples obtained from 12 patients sporadically examined (although at least once during the active phase of the affection). There were only 6 samples showing hyperaminoaciduria, obtained from 3 patients. The increased amino-acid excretion was invariably of the 3rd type, and again corresponded with ACTH administration. In no case of this group was hyperaminoaciduria of the R-pattern or the H-pattern found. In the remaining 9 patients the amino-acid level of the urine was normal. Follow-ups in these cases were insufficiently close, however, to warrant definite exclusion of any hyperaminoaciduria. It must be pointed out that 4 of these patients produced a total of 8 urine samples with an aminoaciduria in the high side of normal; these were regarded as borderline cases, for reasons discussed above. Among these nephrotic subjects with normal amino-acid levels there were 2 cases showing the characteristics of glomerular nephritis (profuse haematuria, hypertension and lesions of the ocular fundus; marked and constant decrease of inulin clearance in one case), and 1

case showing a condition combining a nephrotic syndrome with Hodgkin's disease.

The above findings, together with the results in Table 1, have been collected in the summarizing Table 2. We have been unable to demonstrate any correlation between the urinary amino-acid level and the haematological and urinary data obtained in these patients. Special attention has been given to albuminuria, calciuria, phosphaturia and Addis' count, and to the blood protein, lipid, calcium, phosphorus and alkaline phosphatase values. The number of complete ionograms available, however, is too small to warrant any conclusion as regards either urine or blood in this respect.

Discussion

Our observations primarily confirm the literature reports stating that lipid nephrosis may run its course without ever showing hyperaminoaciduria. In our series this was seen not only in favourable cases showing a remission within a short time, but also in patients with chronic recurrent lipid nephrosis requiring prolonged ACTH therapy. Among these patients, in whom no aminoaciduria was observed at all, there was one fatal issue (the patient also suffering from Hodgkin's disease). At the time of reporting, moreover, two of these patients show unmistakable signs of chronic glomerular nephritis. A normal amino-acid excretion, therefore, does not by any means imply a favourable prognosis. These observations correspond with findings reported by all investigations concerned with glomerular nephritis, with or without a nephrotic syndrome (4, 11, 24).

In some peculiar, severe cases of lipid nephrosis we found the very characteristic

TABLE 2. Overall results.

Number of urine specimens	With normal aminoaciduria		With hyperaminoaciduria			3rd type	Total
	Transient	Constant	R-pattern		H-pattern?		
1st Group:							
Urine specimens from the 10 patients in Table 1	16	15	5	11	3	8	58
2nd Group:							
Urine specimens from the other 12 patients		19	—	—	—	6	25
Total							
Urine specimens from 22 patients		50	16		3	14	83

hyperaminoaciduria described by Woolf & McC.Giles (1956) as R-pattern. Although our series is limited, yet we tend to agree with the English authors that an unfavourable prognostic significance must be attached to it, as 2 of the 3 patients in question died. Yet in the 3rd patient we saw complete clinical and serological remission following prolonged ACTH therapy—a type of development not mentioned by Woolf & McC.Giles, but probably also seen by Squire *et al.* (1957). The small number of R-patterns seen in our series is probably correlated with the low mortality, viz. 3 patients out of 22, as against 8 cases in a series of 28 described by Woolf & McC.Giles. On the basis of data presented by Blainey (1955) and Shreeve *et al.* (1955), this typical hyperaminoaciduria is also likely to occur in adult patients suffering from “nephrosis”, in whom this affection is often a result of severe irreversible renal damage of established aetiology.

With regard to the pathogenesis of hyperaminoaciduria showing the R-pattern, the hypothesis forwarded by Woolf &

McC.Giles (1956) would seem to be the most plausible. They attribute this excessive amino-acid excretion to insufficient reabsorption from the glomerular filtrate at the level of the proximal nephron. This hypothesis is supported in our personal observations on this type of hyperaminoaciduria in 2 patients (out of 3), as they show other signs of tubular insufficiency. In patient Armand de T... there was renal glucosuria and a decreased phosphate reabsorption. In patient Ghislain de B... there were similar changes, with in addition all the clinical and biochemical symptoms of the de Toni-Debré-Fanconi syndrome (Hooft & Vermassen, 1958). Direct proof of a disturbance in amino-acid reabsorption was presented only in a case of nephrosis in an adult patient (Shreeve *et al.*, 1955). For the time being, therefore, indirect proof in favour of the hypothesis of Woolf & McC.Giles must suffice, viz (a) the possible combination with other signs of tubular insufficiency, e.g. renal glucosuria and increased phosphate clearance, (b) marked similarities between blood and urine chromatograms, and (c) the absence

of any hyperaminoacidaemia (in some cases even decreased blood amino acid levels), as against massive hyperaminoaciduria.

The last point in particular merits some elucidation. As regards the blood amino acid levels, the majority of authors conclude that it is never increased but often decreased, particularly in chronic nephrosis (12, 28, 30, 35). With the exception of Farr & MacFadyen, however, none of these authors reports on a systematic investigation over prolonged periods of observation. The results obtained by the various authors cannot be compared in any case due to differences in techniques used.

We have carried out a few random tests, using both paper chromatography and the Antener (1951) method of α -amino nitrogen determination, among our patients with the R-pattern. Paper chromatography revealed transient global hypoaminoacidaemia in 5 samples obtained from 2 patients. In the same group of patients total α -amino nitrogen determinations were made 10 times; in 3 instances there was hypoaminoacidaemia varying from 2.6 to 5.4 mg/100 ml (normal in our laboratory: 6-8 mg/100 ml).

In patient Eric D..., ascites and hydrothorax fluid was also examined. In accordance with expectations concerning a blood ultrafiltrate, an amino-acid pattern was found which was highly similar to that of the blood chromatogram. In addition, it greatly resembled the urinary chromatogram with the R-pattern obtained in the same patient. Thus there are indications suggesting a renal origin of hyperaminoaciduria showing the R-pattern. It should be borne in mind, however, that our results in this group do not deviate from what was found in blood and transudates from other nephrotic patients.

With regard to hyperaminoaciduria not showing the R-pattern it should be

pointed out that only one patient, in the course of a manifest infectious hepatitis, showed a hyperaminoaciduria resembling the H-pattern of Woolf & McC. Giles (1956); this contrasts with the frequent occurrence of this type in the material described by the English authors. Consequently we are unable to form an opinion as to their hypothesis that this should be interpreted as an expression of a functional hepatic disturbance in lipoid nephrosis. This possibility has been discussed by one of us in a previous publication, on the basis of an investigation into various liver function tests. Details can be found in this publication (Hooft & Clara, 1954). It would appear difficult to us to confer any pathognomonic value to urinary chromatograms with the H-pattern, as the literature on amino acid levels in hepatic diseases has not reached unanimity (4, 10, 22, 42).

The interpretation of the third type of hyperaminoaciduria encountered in the course of this investigation is equally difficult. In order to solve the question of a possible correlation with ACTH-therapy, an untreated control series of absolutely identical composition should be available. Since we are confronted with a complete impossibility in this respect, we must rely on the clinical and experimental findings concerning the general action of ACTH and glucocorticosteroids on the blood and urine amino-acid concentrations. Publications on this subject invariably mention hyperaminoaciduria, although of varying intensity and duration (6, 27, 29, 31). We have often observed this effect in patients not suffering from lipoid nephrosis. There is an unmistakable correlation with the dose administered: in two patients, one

with idiopathic hypoglycaemia and another with adrenogenital syndrome, there was no demonstrable hyperaminoaciduria during treatment with 10 mg prednisone daily for several months. In two other patients, one with dermatomyositis and another with rheumatoid arthritis, there was a considerable increase in amino-acid excretion in the course of equally prolonged treatment with large doses (up to 150 mg ACTH and 40 mg prednisone daily).

With regard to lipid nephrosis, the effect of ACTH on amino-acid levels has hitherto been described only in one case (by Schreier & Sattelberg, 1951): a hyperaminoaciduria was elicited. The pattern in these cases of ACTH-hyperaminoaciduria, although not pathognomonic of this hormonal action, is clearly distinguishable from the characteristic patterns described by Woolf & McC.Giles (1956). We are not informed of any investigation into the exact mechanism of hyperaminoaciduria following administration of ACTH or glucocorticosteroids. On the basis of physiological considerations a prerenal influence on the protein metabolism has been held responsible so far, at least partly. After administration of these hormones there is in fact as a rule a moderate increase in the blood amino-acid level. The

number of determinations available to us before and after ACTH therapy is not sufficiently large to warrant any conclusion in this respect. It should be borne in mind, moreover, that this increase might be relative, and that hormonal treatment might return the blood amino-acid level, which is often low in the case of lipid nephrosis, to normal limits.

Conclusion

The urinary excretion of amino-acids is as a rule normal in children suffering from lipid nephrosis. Intercurrent diseases and treatment with ACTH or glucocorticosteroids, however, may influence this excretion.

In a few cases, moreover, typical hyperaminoaciduria (R-pattern) was found independently of any therapy; this probably indicates a tubular dysfunction, and it may occur in combination with renal glucosuria and decreased phosphate reabsorption. The clinical course in the patients showing hyperaminoaciduria with the R-pattern differed from that in the classical form of lipid nephrosis. In one case it was characterized by the occurrence of the complete syndrome of de Toni-Debré-Fanconi, and in the remaining two by a difference in the response to ACTH therapy.

Summary

In a paper chromatographic study of aminoaciduria in the course of lipid nephrosis in children, the authors followed closely 10 patients (58 urine samples), and occasionally 12 others (25 urine samples). In the active stage before treatment, either a normal aminoaciduria or a very characteristic kind of hyperaminoaciduria, already described by Woolf & McC.Giles (1956) as R-pattern, was found. This peculiar hyperaminoaciduria clearly belonged to special types of lipid nephrosis. One patient developed the complete picture of the de Toni-Debré-Fanconi syndrome. The two others did not respond in the

usual way to an early course of ACTH in high dosage, one of them showing furthermore definite signs of tubular dysfunction. The patients with normal aminoaciduria were favourable cases of short duration as well as chronic cases, some of them even showing symptoms of glomerular nephritis or associated Hodgkin's disease (1 case). Only one of these patients developed the second type of hyperaminoaciduria described by Woolf & McC.Giles (H-pattern): it occurred exclusively during manifest infectious hepatitis. The same patient and a few others in this group also developed a definite hyperaminoaciduria under ACTH treatment, which could easily be distinguished from the two above-mentioned patterns, and which is referred to in this paper as 3rd type. It did not occur in every patient treated by ACTH. The authors discuss the pathogenesis of the three types of hyperaminoaciduria encountered, on the basis of the literature reviewed and of their own observations, chiefly on blood amino-acid levels and associated symptoms of renal tubular dysfunction.

L'aminocidurie au cours de la néphrose lipéidique chez l'enfant. L'influence de l'ACTH.

Les auteurs ont étudié à l'aide de la chromatographie sur papier l'aminocidurie au cours de la néphrose lipéidique chez l'enfant. 10 malades ont été suivis de près (58 échantillons), et 12 autres occasionnellement (25 échantillons). Au cours d'une phase active et avant tout traitement, ils ont trouvé soit une aminocidurie normale, soit une hyperaminoacidurie très caractéristique, déjà décrite par Woolf & McC.Giles (1956) sous la dénomination de « R-pattern ». Cette hyperaminoacidurie se rattachait de façon distincte à des cas très particuliers de néphrose lipéidique. Un des malades a évolué vers un syndrome de de Toni-Debré-Fanconi absolument complet. Les deux autres n'ont pas présenté la réponse habituelle au traitement par l'ACTH à forte dose, appliqué au début de la maladie. Chez l'un d'eux par surcroît, d'autres perturbations des fonctions tubulaires ont été démontrées. Parmi les malades avec aminocidurie normale, l'on trouve aussi bien des cas favorables et de courte durée, que des cas à évolution chronique, dont certains présentent des symptômes de glomérulonéphrite ou même d'une association avec la maladie de Hodgkin (1 cas). Un seul de ces malades a présenté par après le second type d'hyperaminoacidurie décrit par Woolf & McC.Giles (H-pattern): à ce moment, il existait une hépatite infectieuse cliniquement manifeste. Ce même malade et certains autres du même groupe ont présenté également une hyperaminoacidurie indiscutable sous traitement par l'ACTH. La distinction par rapport aux deux autres types d'hyperaminoacidurie déjà cités était aisée, et nous l'avons simplement désignée comme « 3^e type ». Cette hyperaminoacidurie n'apparaît cependant pas chez tous les malades traités par l'ACTH. Les auteurs discutent ensuite la pathogénie des trois types d'hyperaminoacidurie qu'ils ont rencontrés, se basant sur les données de la littérature et sur leurs propres observations, concernant surtout l'hyperaminocidémie et la coexistence d'autres symptômes d'une dysfonction tubulaire du rein.

*Über die Aminoacidurie bei der Lipoidnephrose des Kindes.
Einfluss der ACTH-Behandlung.*

In einer papierchromatographischen Studie über die Aminoacidurie bei der Lipoidnephrose des Kindes habe Verf. 10 Patienten sehr genau (58 Urinproben), und 12 andere nur gelegentlich (25 Urinproben) verfolgt. Im aktiven Stadium vor jeglicher Behandlung wurde entweder eine normale Aminoacidurie gefunden, oder eine sehr kennzeichnende Hyperaminoacidurie, die schon von Woolf & McC.Giles (1956) als „R-pattern“ veröffentlicht war. Diese eigentümliche Hyperaminoacidurie ist offenbar mit Sondertypen der Lipoidnephrose verbunden. Ein Patient hat ein typisches de Toni-Debré-Fanconi-Syndrom entfaltet. Die anderen zwei reagierten nicht in der üblichen Weise auf eine Frühbehandlung mit hohen Dosen ACTH, und einer davon wies zudem andere Störungen der Tubulustfunktionen auf. Unter den Patienten mit normaler Aminoacidurie findet man sowohl günstige und kurzfristige wie auch chronische Fälle; einige davon zeigten sogar Symptome der Glomerulonephritis oder des Mb. Hodgkin (1 Fall). Nur einer dieser Patienten hat nachträglich eine Hyperaminoacidurie des zweiten Typus (Woolf & McC.Giles) aufgewiesen (H-pattern): sie ist jedoch nur während einer manifesten Hepatitis infectiosa aufgetreten. Derselbe Patient und einige anderen in dieser Gruppe wiesen auch unter ACTH-Behandlung eine bestimmte Hyperaminoacidurie auf; diese war leicht von den beiden anderen Typen zu trennen und wurde in dieser Arbeit als „3. Typ“ bezeichnet.

Das Auftreten dieser Hyperaminoacidurie war auf einige der ACTH-Patienten beschränkt. Verff. erörtern die Pathogenese dieser drei Typen von Hyperaminoacidurie unter Berücksichtigung des Schrifttums sowie eigener Beobachtungen, insbesondere über den Blutspiegel der Aminosäuren und über etwaige gleichzeitig gestörte Tubulusfunktionen.

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Kliniek voor Kinderziekten
Pasteurdreef 2
Gent, Belgium

Renal Function in Water-Losing Syndrome Due to Lower Urinary Tract Obstruction Before and After Treatment

by JAN WINBERG

Congenital obstruction of the lower urinary tract with hydronephrosis is practically always complicated by pyelonephritis at a very early age. It is therefore impossible to decide the relative importance of hydronephrosis and infection in causing the severe renal damage which leads to renal insufficiency and early death in most of these cases (Campbell, 1951).

Some suggestions concerning the effect of hydronephrosis and obstruction *per se* on renal function might be made from a study of some aspects of renal function in a 13-year-old boy with large bilateral hydronephrosis and without any history or signs of previous infection. A study of another case, which, however, had a urinary tract infection, is thought to throw some more light on the problem under discussion.

Case Reports

CASE 1.—O. H. Boy, 13 years old, admitted because of polyuria and polydipsia. Hereditary history irrelevant. Stature always small, otherwise normal development. Normal physical and mental activity. Controlled bladder at the age of 2 years. Nocturnal enuresis began at the age of 4 years, diurnal at the age of 7. These symptoms persisted unchanged until admission. Micturition otherwise normal. Never any symp-

toms of urinary tract infection. Repeated examinations had failed to show any abnormal urinary constituents. Since the age of four years the patient had consumed large quantities of water daily, and in the last years as much as 1-2 liters every night. The parents had been told that his polydipsia was only a bad habit.

On examination at the age of 13 years the patient was in good general condition. Height 131 cm (normal variation ± 2.5 δ -limits 134-173 cm for the age), weight 31.1 kg (normal variation in relation to length ± 2.5 δ -limits 22-33 kg). Bladder palpable at the level of the umbilicus after micturition. Blood pressure 125/80 mm Hg. Eye grounds normal. Roentgen of the skeleton, including sella turcica, normal.

Urological data. Urine volume 5.5-6 liters/24 hours, specific gravity usually 1.002-1.004. After water deprivation for a few hours he became pale, tired and irritable and experienced an intractable thirst. Pitressin without effect on urinary concentration. There was no albuminuria and no reducing substance in the urine. Urinary sediment normal, urine culture negative. Serum electrolytes normal.

Intravenous urography showed the kidneys to be of normal size. The pelvices and ureters were enormously dilated and the renal parenchyma thin (Fig. 1A). On micturition urethrocytography the bladder was shown to be large and raised. No vesico-ureteral reflux. In the posterior urethra there was a valve causing a marked obstruction

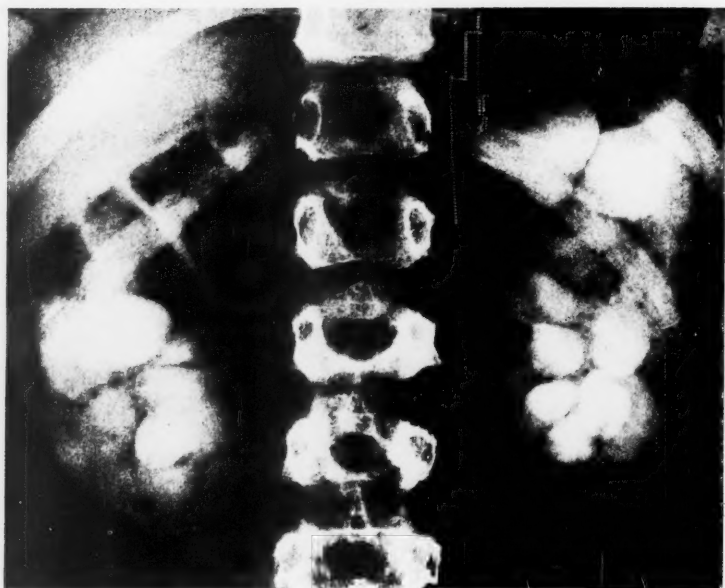


Fig. 1A. Case 1. Preoperative i.v. urography, Sept. 18, 1957. Bilateral hydronephrosis and hydroureter. Calices and the ampullar part of the pelvis are markedly dilated in both kidneys. The renal parenchyma is thin. The concentration of the contrast medium is lowered.

to the urinary flow (Fig. 2A). The residual urine amounted to about 400 ml. Urethrocytoscopy showed both ureteral orifices to be of normal appearance. A transurethral resection of the valve was performed. Postoperative urethrocytography demonstrated that the valvular obstruction was completely removed, and that the urinary flow was free (Fig. 2B). There was no residual urine. On intravenous urography 9 months later there was regression of the dilatation of the pelvices and calices (Fig. 1B).

No enuresis postoperatively. The urine volume 9 months postoperatively was about 3-4.5 liters per 24 hours. Administration of pitressin tannate twice a week reduced the urinary output to about 1.0-1.5 liters per 24 hours. During the urological investigation he contracted a urinary tract infection. *Staph. aureus*, coliforms and *Pseudomonas aeruginosa* were cultured. The *Pseudomonas* infection persisted 9 months postopera-

tively but gave no clinical symptoms. The results of the renal function tests are described below.

To summarize, this is a case of congenital obstruction of the lower urinary tract, with resulting bilateral hydronephrosis, presenting symptoms as a case of diabetes insipidus. Postoperatively there was a considerable improvement of the water-conserving capacity. It is probably unique for such a case not to have contracted a urinary tract infection until the age of 13 years.

CASE 2.—E. W. Girl, 9½ years old, admitted because of a longstanding urinary tract infection. Symptoms suggestive of cystitis at the age of 4 years. Since that time periods of nocturnal and diurnal enuresis, sometimes in connection with pyuria. First

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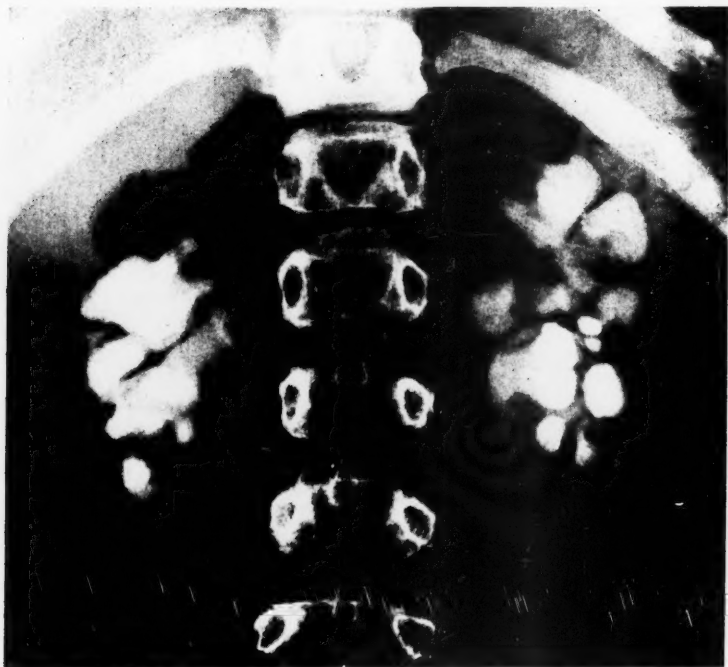


Fig. 1B. Case 1. I.v. urography 9 months after operation, June 17, 1958. There is a clear regression of the hydronephrosis bilaterally and an increased concentration of the contrast medium in the urine. The ureters are still dilated and tortuous.

acute, febrile urinary tract infection at the age of 9 years. At that time, intravenous urography showed a slight dilatation of the distal parts of the ureters but was otherwise normal (Fig. 3A). Residual urine 300 ml, but no obstruction of the urethra. Rapid improvement after antibacterial treatment.

The last months before admission to our clinic the parents noticed the girl to have an increased thirst. On admission at the age of 9½ years she was found to be normally developed but she was pale and thin. Bladder palpable 3 cm below the umbilicus. Blood pressure 140/100 mm Hg. Neurologic investigation normal.

Urological data. The 12-hour urinary volume varied between 1000 and 1400 ml, specific gravity 1.004–1.008. The patient could withstand a 16-hour thirst period.

Decreased sensitivity to pitressin. The urine exhibited traces of albumin, no reducing substance, periodical pyuria and bacteriuria. Serum electrolytes normal.

Intravenous urography showed the kidneys to be of normal size. Definite dilatation of pelvices and ureters on both sides. On the left side a moderate reduction of the renal parenchyma (Fig. 3B). The hydronephrosis thus had developed during the last 8 months. On control 2 months later after indwelling catheter had been applied for 3 weeks there was a marked regression of the hydronephrosis (Fig. 3C). On micturition urethro-cystography no infravesical obstruction was found and no vesico-ureteral reflux. The bladder picture, however, was similar to that found in neurogenic disturbances. On urethro-cystoscopy the ureteral outlets were



Fig. 2A. Case 1. Preoperative micturition urethrocytography, lateral view, Sept. 7, 1957. The internal urethral orifice and the posterior urethra down to an obstructing valve are dilated. The valve is situated close to the colliculus seminalis and constricts the urethra from in front and laterally. The valvular ostium situated dorsally is narrow. Distal to the valve the widening of the urethra is incomplete. The bladder is large, raised and trabeculated. No vesico-ureteral reflux is present.

found to be normal and not strictured. Cystometrogram showed no miction pressure. The patient probably emptied her bladder mainly by straining. This might account for the fact that sometimes there was no residual urine, and other times it was up to 300 ml. The patient was treated with a periodic indwelling catheter. As will be described below there was a marked improvement of renal function during this time. The thirst diminished, appetite improved

and the patient increased 10 kg in weight during 4 months.

To summarize, this was a case of retention due to a neurogenic bladder disturbance of unknown etiology and duration. The accompanying hydronephrosis had been present for less than 8 months before the renal function studies began. As far as is known the patient had had only one

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Fig. 2B. Case 1. Postoperative micturition urethrocytography; lateral view. Dec. 2, 1957. No valve residual visible. The internal urethral orifice and the urethra looks normal during micturition. The bladder is still large and trabeculated. No vesico-ureteral reflux is present.

acute, febrile urinary tract infection. During the investigation there was a chronic, non-symptomatic infection. Since questions concerning etiology, treatment and prognosis are irrelevant for the problems under discussion in this article they will not be further considered.

Methods

Endogenous creatinine in plasma and urine was determined after extraction with Lloyd's reagent according to the method described by Hare. Readings were made on a Beckman B spectrophotometer. The clearance of endogenous creatinine, here called C_{CR} , thus analyzed, is by most authors supposed to give clinically useful informa-

tion about the glomerular filtration rate in cases where renal function is not seriously damaged (1, 2, 10, 15). Some authors, however, are critical of this method in chronic renal disease (19). Although subject to some criticism C_{CR} is used in the following as a measurement of glomerular filtration rate. Blood samples for plasma creatinine determination were drawn in the morning during fasting conditions. Urine was collected during 24-hour periods. The method will be closer discussed in a subsequent paper.

The pH of urine was determined with a Beckman pH-meter. The osmolality of urine was calculated from the freezing point depression determined with the aid of a thermistor and a Wheatstone's bridge. The osmolality was determined with an accuracy of ± 5 mOsm/kg H_2O . Ammonia was esti-



Fig. 3 A.

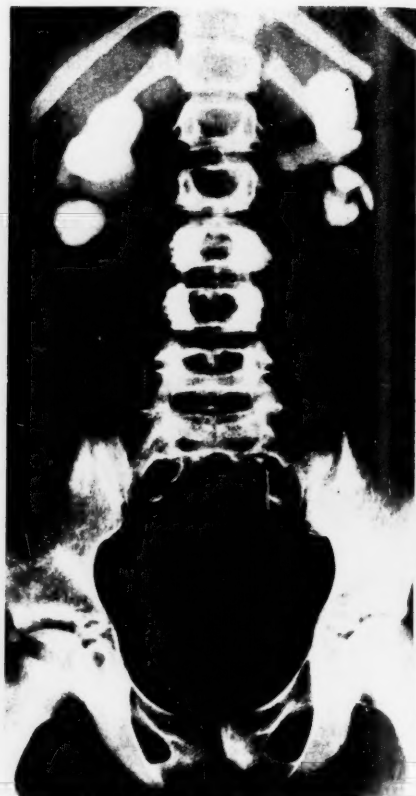


Fig. 3 B.

Fig. 3. Case 2. Intravenous urography. (A) May 16, 1957. The renal pelvises are bilaterally normal in shape and width. The distal parts of the ureters are slightly dilated. (B) On first admission, December 10, 1957. The renal pelvises and the ureters are now definitely dilated.

mated according to Conway, using the micro diffusion technique with absorption in boric acid solution and titration with 0.1 *N* acid from the "Aglä" micrometer syringe. The error of method was 0.97 per cent. Titratable acidity was determined with phenolphthalein as an indicator during titration with 0.1 *N* NaOH. This method yielded higher values than titration to an electrometrically determined endpoint of pH 7.4.

Results

Results of the renal function studies in Case 2 will be given only in so far as they

are of interest to the present discussion of the effect of obstruction on urinary function.

Glomerular Function

CASE 1. There was no marked reduction of C_{CR} either preoperatively or when estimated 2, 4 and 9 months postoperatively (Table 1). Administration of probenecid, 500 mg daily, for four days did not lower the creatinine clearance or increase plasma creatinine concentration.

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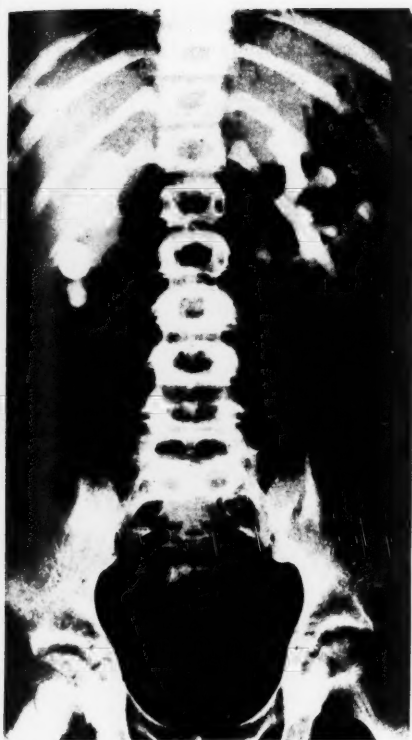


Fig. 3 C. After 3 weeks of bladder drainage, Feb. 10, 1958. Marked regression of the dilatation of the left renal pelvis. The dilatation of the right pelvis and both ureters is essentially unchanged.

the plasma concentration of creatinine (cf. Hare) glomerular filtration rate probably cannot have been markedly reduced (cf. Steinitz & Türkand).

CASE 2. In all periods urine collection was performed by means of indwelling catheter. In this case, as in the preceding there was no appreciable reduction of glomerular filtration rate.

Probably there was a slight increase in C_{CR} when determined before and after a 6-week-long period of continuous cath-

terization of the bladder, but it cannot be decided whether this was due to relief of obstruction or improvement of infection.

Renal Base Conserving Capacity

CASE 1. During the pre- and postoperative investigations the patient had a bacteriuria. Since there were no indications for bacterial ammonia production this is thought not to invalidate the results obtained. Preoperatively, urine pH was checked twice daily, at 11 A.M. and 4 P.M., about 4 hours after the preceding NH_4Cl administration. Meals were served at 8 A.M. and 2.30 P.M. Postoperative pH (Fig. 4) refers to the 24-hour volume, and on two occasions to fasting values obtained at 8 A.M., two hours after the preceding administration of NH_4Cl .

Urinary hydrogen ion concentration. Preoperatively, the lowest urine pH observed during the first $2\frac{1}{2}$ days of an acid load was 5.84 (Fig. 4). Potassium depletion (Clarke, Evans, Macintyre & Milne) could not account for the defect in urinary acidification, since supplementary K was rapidly excreted and did not appreciably affect urinary pH (Fig. 4). Four months postoperatively, pH values of 5.19 and 5.20 were observed on two different acidification tests. Nine months postoperatively (Fig. 4) the lowest pH observed was 4.9. The preoperative pH is 0.7–1.2 units higher than those found by Wood and Clarke *et al.* after acidification and indicates an inability of the distal tubules to establish a maximal concentration gradient of H^+ between the tubular cells and tubular urine. The damage seems to be, at least partly, reversible. Since urine volumes during the acidification tests were about the same pre- and postopera-

TABLE 1. *Endogenous 24-hour creatinine clearance.*

Investigations in Case 1, performed two and four months postoperatively, gave similar results as preoperatively.

	No. of consecutive 24-hour collection periods	Endogenous plasma creatinine mg/100 ml	Mean C_{CR} ml/min/1.73 sq.m.
CASE 1			
Months post-operatively			
0	2	0.74 0.77 0.69	85
1	1	0.62	89
9	7	0.74 0.70	87
CASE 2			
Days of drainage before urine collection			
3	3	0.62	85
0	4	0.71 0.75	79
40	4	0.54 0.53	100
0	4	0.69 0.73	94

tively, the increase in H^+ concentration cannot be explained as due to secretion of a more concentrated urine.

Ammonia. Preoperatively urinary ammonia concentration was determined twice daily and the concentration of the 24-hour volume calculated from these values. Postoperatively ammonia was determined on the 24-hour volume.

As seen in Fig. 4, there is an appreciable increase of ammonia excretion during the acid load both pre- and postoperatively. The temporary depressions in ammonia

excretion seen preoperatively are caused by potassium administration.

Normal values for ammonia excretion during an acid load are scarce. The increase observed in the present case is of the same magnitude as in some of the normal cases reported by Clarke *et al.*

Thus there is an incapability to excrete a highly acid urine but an apparently normal capacity for ammonia production.

Renal Concentration Capacity

CASE 1. As demonstrated in Fig. 5, the concentration defect in this case was resistant to i.m. Pitressin. This was tested four times with negative result each time. Two months postoperatively there was a good response to Pitressin. At a new postoperative examination performed 4 months after resection of the valve there was only a slight and late increase in urinary osmolality, but a few days later pitressin caused a marked increase in urine concentration (Fig. 5). Nine months postoperatively a urinary osmolal concentration of 576 mOsm/kg was observed. At this time the patient, when forced, could withstand water deprivation from 8-10 hours without becoming ill.

In spite of this improvement the patient continued to drink water freely and excrete 3.0-4.5 liters of urine daily. With the aid of pitressin tannate in oil, the 24-hour urine volume was brought down to between 1000 and 1500 ml.

CASE 2. The concentration tests were performed as follows. At 4 P.M. the patient was given 0.3-0.4 ml of pitressin tannate in oil intramuscularly, and fluids were withheld until about 9 o'clock the following morning. Urine was collected during

Fig. 4. Filtered, supplemented, carbonated pH of urine.

Fig. 5. before

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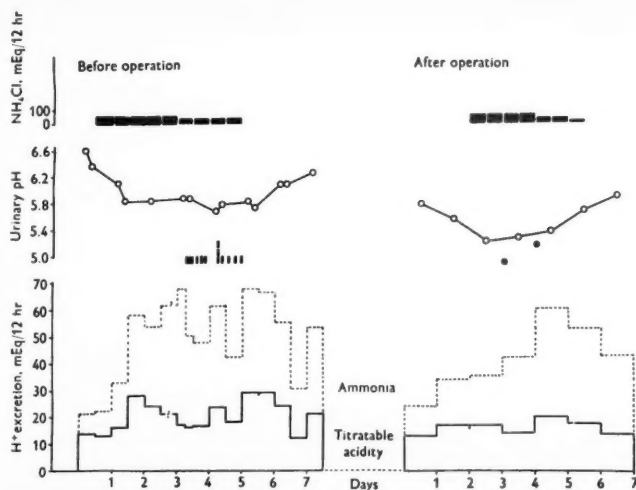


Fig. 4. Case 1. Acidification test before and 9 months after operation. Ammonium chloride administered with 6 hours' interval. Lowest urinary pH before operation 5.68, after operation 4.9. Potassium supplement caused a depression in ammonium excretion, but no appreciable lowering of pH. Serum carbon dioxide combining power during the 4th day of acidification 12 mMol/l. O, preoperatively: pH of random samples (see text); O, postoperatively: pH of 24-hour volume; ●, pH of fasting morning urine; ■, oral ingestion of 13.4 mEq of KCl. Broken line gives total H^+ excretion. The area between broken and solid lines indicates ammonium ion excretion.

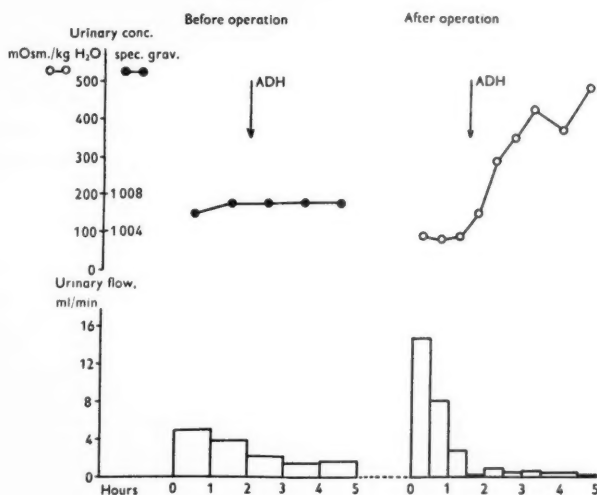


Fig. 5. Case 1. Response to pitressin before and four months after operation. The patient was hydrated before beginning of urine collection. Arrow indicates intramuscular injection of 10 P.U. of pitressin in aqueous solution.

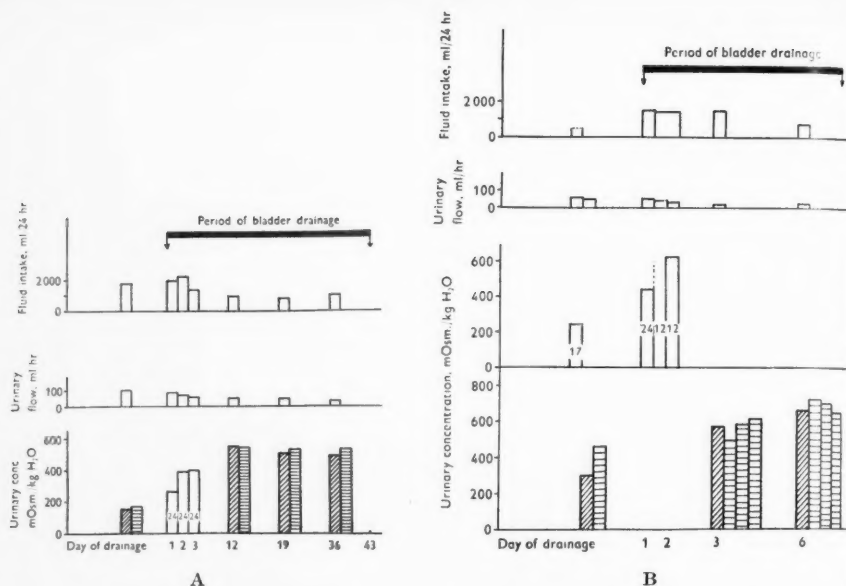





Fig. 6. Case 2. Urinary concentration before and during continuous drainage of the bladder.

(A) Before and during a 6-week period of catheterization. It is seen that the osmolal concentration of the 24-hour volumes immediately after catheterization is considerably higher than during a pitressin test (see text) before.

(B) Two months after cessation of previous drainage. Starting values better than in preceding investigation. Figure shows again the rapid influence of drainage on concentration capacity.

-  Osmolal concentration of night urine during pitressin test.
-  Osmolal concentration of morning urine (16–18 hours of water deprivation) during pitressin test.
-  Osmolal concentration of daily urine volume without thirst or pitressin. Figure within bar gives duration of collection period.

the night and during one or more 1-hour periods the following morning.

When this procedure was applied to the patient on two different occasions the highest urinary concentration observed was 171 mOsm/kg and 280 mOsm/kg respectively. Because of large residual urine the bladder was continuously drained by an indwelling catheter for 3 weeks. After 6 days of drainage, the concentration of two random urine samples, obtained without

thirst or pitressin, was 370 and 367 mOsm/kg respectively. The finding was judged as a probable improvement of the concentration capacity.

The investigations demonstrated in Figs. 6A and 6B were undertaken to reproduce the above finding and determine the duration of continuous bladder drainage necessary to improve the concentration capacity.

It is seen in Fig. 6A that the maximal

urinary concentration observed during a pitressin test before the catheterization period was only 172 mOsm/kg, while the concentration of the 24-hour volumes obtained during the first three days of catheterization increased from 266 mOsm/kg to 395 mOsm/kg. Fluid intake was essentially unchanged, urine volumes were diminished. Pitressin tests performed during the period of bladder drainage showed very constant urinary concentrations, which were appreciably higher than during the predrainage period.

The investigations illustrated in Fig. 6B were performed when the patient was much improved, probably as a result of the preceding long drainage period. It is seen that the urinary concentration in a 17-hour volume (including night) preceding catheterization is definitely lower than the concentrations during the two days immediately after catheterization, in spite of a water load during these last-mentioned periods. Post-catheterization pitressin test again demonstrated a rapid improvement of concentration capacity.

During these investigations the patient was subject to a low grade, chronic urinary tract infection.

Comment

Since lower urinary tract obstructions with hydronephrosis in children almost always are complicated by pyelonephritis, the first case described in this paper presents an almost unique opportunity to study the effect of pure obstruction on renal function.

The functional changes demonstrated in this case consist of a pitressin-resistant polyuria with excretion of a hypotonic urine and a decreased ability to produce a

highly acid urine. Ammonia production and glomerular filtration rate were not appreciably diminished.

The changes were interpreted as due to the effect of obstruction. A nonsymptomatic infection, acquired during the stay in hospital a few days before the acidification test, was thought to have little effect upon renal function. This was supported by the fact that, in spite of persisting infection, the renal function improved after relief of obstruction.

Hypotonic polyuria as a result of obstruction, has earlier been demonstrated by Roussak & Oleesky in an old man with prostatic enlargement and noninfected hydronephrosis. Kerr (17, 18) and Widén (29) found a decreased concentration capacity in the presence of normal dilution capacity after a period of complete ureteral obstruction in dogs. Kerr (18) found this concentration defect to persist even after complete restoration of glomerular filtration. This indicates, as in the two cases described here, that obstruction causes a more serious damage to that part of the nephron responsible for the concentration of urine than to the glomeruli. This is in accordance with histologic investigation in animals showing the glomeruli to be more resistant to the effect of obstruction than the tubules (7, 16, 20, 22, 28, 30 and others).

The demonstration in Case 1 of a decreased ability to excrete a highly acid urine suggests a damage mainly of the distal tubules where the secretion of H^+ takes place. In view of the fact that H^+ and NH_3 are added to the urine in the same place (Pitts, Gurd, Kessler & Hierholzer) the dissociation found between these two functions is somewhat confusing.

However, morphologic investigation in various species with experimental hydro-nephrosis have consistently shown that the hydronephrotic atrophy is characterized by a group resistance and group atrophy of nephrons possibly related to impeded blood supply (Hinman & Hepler, Hinman & Morrison).

This might provide an explanation of the dissociation found between ammonia excretion and ability to lower the pH of urine. Bladder urine, obtained during an acidification test, could be a mixture of a highly acid urine derived from relatively intact nephrons and a more alkaline urine secreted by damaged nephrons, incapable of establishing a high H^+ concentration gradient across the cellular membrane of the distal tubular cells. Since remaining nephrons are capable of hypertrophy (Hinman) it does not seem impossible that the preserved nephrons would be capable of secreting the same amount of ammonia as an intact kidney.

The excretion of a hypotonic urine during pitressin-induced antidiuresis deserves some comment. The way in which the kidneys change the isosmotic glomerular filtrate to a hypo- or hypertonic urine has been the object of discussion and experimental work, i.e. by Smith (25, 26) and Wirz (32, 33). Both authors agree that a hypotonic urine is elaborated by an active reabsorption of sodium; also, under the influence of antidiuretic hormone, the osmotically liberated water is thought to be reabsorbed within the distal tubules by a passive diffusion along osmotic gradients; an isosmotic urine then enters the collecting ducts. Sawyer has proposed that the antidiuretic hormone exerts its characteristic effect by increasing the pore size of

the epithelium of the distal tubules, thus making them more permeable to water.

If the above considerations are valid the excretion of a hypotonic urine after administration of antidiuretic hormone indicates a damage of the distal tubular cells, that has made them highly impermeable to water. Since the distal tubular water reabsorption forms the quantitatively more important contribution to water economy a damage here will mask the effect exerted by the collecting ducts on water balance. Therefore, it cannot be decided whether in the present cases there was a damage only of the distal tubular function or if also the collecting ducts were damaged.

Although there was an increased ability to concentrate the urine after relief of obstruction, the patient continued to excrete large urine volumes. Since these volumes were reduced almost to normal after administration of long-acting pitressin the postoperative polyuria and polydipsia could not be "psychogenic". One explanation of the persisting polyuria would be that obstruction had caused such a damage of the distal tubular cells that they did not reabsorb water efficiently until the plasma concentration of antidiuretic hormone was raised above the normal. In view of the demonstration by de Wardener & Herxheimer that compulsive polydipsia will cause a decreased renal ability to concentrate urine, another explanation of the persisting polyuria in the present case would be that the high water intake of many years' duration had in itself caused a defect in renal water conservation capacity.

If we turn to Case 2, the rapid, though incomplete, reversibility of the concentra-

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tion defect after bladder drainage shows that there cannot be severe structural changes causing this disturbance. The findings suggest that the damage was mainly of functional nature in this patient whose hydronephrosis was of short duration.

Animal experiments similar to that in Case 2 have been performed earlier. By direct measurement performed in perfusion experiments on rabbits, Ghoreyeb and Idbohrn & Muren have demonstrated a rapid decrease of renal circulation after ureteral obstruction. Ghoreyeb found that when the obstruction was relieved by direct puncture of the renal pelvis, there was a rapid increase in the renal circulation, sometimes within a few minutes.

If the findings in Case 2 are considered together with the supposed importance of tissue ischemia for the development of the hydronephrotic atrophy and with the

findings by Ghoreyeb and Idbohrn *et al.*, it does not seem improbable that the damage of the distal tubules (and of the collecting ducts?) is due to interference with the blood supply of these parts of the nephron. Such a hypothesis conforms well with the rapid improvement of the concentration capacity. It cannot be excluded, however, that other factors, such as distension of the tubules or direct influence of the increased intrarenal pressure on the tubular cells, are responsible for the functional changes observed.

Although conclusions from single cases necessarily must be guarded, it seems likely that the early damage of glomerular function in congenital bilateral hydronephrosis (Winberg), and the early uremia and death in such cases (Campbell), in many instances might be due more to the effect of infection than to obstruction.

Summary¹

Renal function studies in a boy of 13 years with earlier noninfected bilateral hydronephrosis due to a urethral valve revealed the presence of a pitressin-resistant hypotonic polyuria and a decreased ability to acidify the urine. Ammonia production and glomerular function were fairly intact. The findings suggest a damage mainly of the distal tubules. Whether there was damage to the collecting ducts cannot be elucidated from the present investigation. After relief of obstruction there was a high degree of reversibility of the functional disturbances in spite of the enormous hydronephrosis present before operation. It is suggested that the uremia and early death common in similar cases during childhood are due more to the effect of infection in these cases than to the hydronephrosis itself.

On the basis of studies in a second case the pathogenesis for the concentration incapacity in hydronephrosis is discussed. No direct answer can be given, but it seems possible that vascular changes followed by nutritional disturbances might play a role.

¹ Since this paper was finished another 14-year-old boy with urethral valve, moderate hydronephroses, hypotonic polyuria and normal C_{CR} has been observed by the author.

La fonction rénale dans le syndrome de déperdition hydrique du à une obstruction urinaire inférieure, avant et après le traitement.

Les études de la fonction rénale pratiquées chez un garçon de 13 ans qui présentait une hydronéphrose bilatérale non-infectée — due à une soupape de retenue au niveau de l'urètre, révéla l'existence d'une polyurie hypotonique résistante à la pitressine avec diminution du pouvoir acidifiant de l'urine. La production d'ammoniaque et la fonction glomérulaire étaient relativement intactes. Ces résultats donnent à penser que les dégâts affectent principalement les tubes urinaires contournés distales. Du reste, même s'il existait une altération au niveau des tubes collecteurs, elle ne saurait être mise en évidence par ce type d'investigation. Après la levée de l'obstacle, les perturbations fonctionnelles furent grandement réversibles, en dépit de la très importante hydronéphrose qui existait avant l'opération. On peut supposer que l'urémie et la mort précoce qui durant l'enfance est habituellement la règle, en ces sortes de cas, est moins la conséquence de l'infection, que de l'hydronéphrose elle-même. A propos d'études portant sur un deuxième cas, la pathogénie du manque de pouvoir de concentration des urines dans l'hydronéphrose est discutée. Aucune réponse formelle ne peut encore être donnée, mais il paraît possible que les altérations vasculaires provoquées pas les troubles de nutrition puissent jouer un rôle.

Die Nierenfunktion bei dem durch Obstruktion der distalen Harnwege hervorgerufenen Wasserverlustsyndrom vor und nach Behandlung.

Nierenfunktionsstudien an einem 13-jährigen Jungen mit nicht infizierter, durch eine Klappe in der Urethra bedingter beiderseitiger Hydronephrose zeigten die Gegenwart einer pitressin-resistenten hypotonischen Polyurie und eine herabgesetzte Fähigkeit, den Harn zu versäuern. Ammoniakproduktion und Glomerulusfunktion waren ziemlich unversehrt. Die Ergebnisse weisen auf eine Schädigung der distalen Tubuli hin. Ob auch eine Schädigung der distalen Sammelgänge vorlag, konnte auf Grund der gegenwärtigen Untersuchung nicht klargestellt werden. Wenn die Obstruktion beseitigt wurde, zeigte es sich, dass die Funktionsstörungen weitgehend rückgängig gemacht werden konnten, trotz der Anwesenheit einer enormen Hydronephrose vor dem Eingriff. Die Vermutung wird ausgesprochen, dass die Urämie und der frühzeitige tödliche Ausgang, die in ähnlichen Fällen bei Kindern gewöhnlich sind, mehr der Einwirkung einer Infektion als der Hydronephrose selber zuzuschreiben sind. Auf Grund von Studien bei einem weiteren Fall wird die Pathogenese der Unfähigkeit bei der Hydronephrose, den Harn zu konzentrieren, erörtert. Es kann keine direkte Antwort auf die Frage gegeben werden, jedoch scheint es möglich zu sein, dass Gefäßveränderungen mit nachfolgenden Ernährungsstörungen eine Rolle spielen könnten.

El estudio de la función renal en un síndrome de pérdida acuosa debido a una obstrucción urinaria baja, antes y después del tratamiento.

El estudio de la funcionalidad renal, en un niño de 13 años, con una hidronefrosis bilateral por válvula uretral, no infectada, reveló la existencia de una poliuria hipotónica pitresina-resistente y una disminución de la capacidad de acidificación. La formación de amoníaco y la función glomerular estaban normalmente conservadas. Los resultados obtenidos sugieren, principalmente, una lesión tubulo-distal. Si ha habido lesión a nivel de los conductos colectores, no se puede elucidar a partir de la presente investigación. Los disturbios funcionales mostraron un alto grado de reversibilidad luego de la eliminación de la obstrucción, a pesar de la enorme hidronefrosis existente previo a la intervención. Se sugiere que la uremia y la muerte temprana, comun en casos similares durante la infancia, sean debidas, más a los efectos de la infección presente, que a la hidronefrosis en sí misma. La patogenia de la incapacidad de concentración en la hidronefrosis es discutida luego del estudio de un segundo caso. A pesar de no poder darse una respuesta directa, parece posible que los cambios vasculares seguidos por transtornos nutricionales puedan ser uno de los factores responsables.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

CASE REPORT

The Simultaneous Occurrence of Congenital Toxoplasmosis and Congenital Myxoedema

by KNUD AAGAARD and JOHANNES MELCHIOR

From the Department of Paediatrics and the Out-patient Clinic for Spastic Children, University Hospital, Copenhagen (Head: Professor P. Plum, M.D.)

In the present paper a case is reported which must probably be interpreted as one of congenital toxoplasmosis without chorio-retinal changes and intracerebral areas of calcification, occurring in an infant with typical congenital myxoedema. The simultaneous occurrence, per se, is of interest as it has been observed previously in a child (Andersen (1)); in this case, however, there was fully developed congenital toxoplasmosis with a fulminant course.

Case History

A boy aged 5 months was admitted in January, 1954, on account of congenital myxoedema.

The boy was the only child of young healthy parents and no endocrine diseases had appeared previously in the family. The pregnancy was the mother's first and she felt perfectly healthy throughout. The delivery occurred 4 weeks later than expected but proceeded naturally with a head presentation. Birth weight: 3500 g. Length: 51 cm. The boy appeared normal at birth, there was no respiratory distress and he did not become jaundiced.

The infant was fed practically entirely on breast milk until the age of 5 months. He

thrived satisfactorily during the first month of life and had begun to smile. Thereafter he did not thrive so well, he became constipated and the mother could no longer elicit a smile. At the age of slightly over 4 months he was admitted to the local hospital from which he was transferred to the Department of Paediatrics.

On admission, the infant measured 54 cm, i.e. 12 cm less than average and weighed 4400 g. The appearance was markedly myxoedematous with coarse features, paleness and a large protruding tongue (Fig. 1). The respiration was grunting and the voice deep, coarse and hoarse. The skin was loose and of a myxoedematous consistence while the eyebrows were sparse.

Circumference of the head: 41 cm. Fontanel: 3×3 cm, not tense. Eyes: no abnormality on general objective examination; pupils reacted normally to light. No epicanthus present. Fauces: normal in appearance. Lymph glands: not enlarged. Thyroid gland: not palpable. Stethoscopy: pulse 92, otherwise no abnormality. Abdomen: rather large with a reducible umbilical hernia, the size of a cherry. Extremities: short with natural tone, no mongoloid furrows. Testes: hydrocele as large as a pigeon's egg on right side, left testis normal on palpation.

Haemoglobin: 9.6 g% (65%). Centres of ossification (Elgenmark's classification (2)):



Fig. 1. 5 months old. Before thyroid therapy was started.

number definitely reduced according to age and height. The additional investigations rendered results as in normal infants and included Wasserman reaction, tuberculin patch test, micro BSR, examination of urine for protein and sugar, microscopy of urine, serum cholesterol, electroencephalography and radiographic examination of the skull.

Therapy with thyroid hormone had the effect anticipated. After therapy for one month when the boy was 6 months old, horizontal nystagmus and alternating convergent strabismus were observed. Ophthalmologic examination revealed clear media and normal eye grounds. At the age of 8 months transient attacks of rigidity and opisthotonus occurred. The circumference of the head was now 45 cm, the body length 66 cm. At this time an investigation for toxoplasmosis rendered a Sabin-Feldman reaction of 1:250-1:1250 and the complement-fixation reaction was 1:4. The same investigation of the mother's serum 10 days, one year and 2 years later rendered on every occasion a Sabin-Feldman reaction of 1:250 and a complement-fixation reaction of 1:2-1:4. On discharge at the age of 9 months (Fig. 2), ophthalmoscopy and radiographic examination of the skull revealed normal conditions as previously; there was no enlargement of the lymph glands.

During the subsequent 3 years the boy was followed up as an out-patient during thyroid therapy. His height remained about 4 cm below average and the rate of growth has thus remained normal. The circumference of the head increased from 2 cm below normal to 2 cm above average for the age in the course of a year and the latter difference has since been maintained. The titre values for toxoplasma antibodies rose gradually until the age of one year and thereafter fell slowly. Findings on radiographic examination of the skull, electroencephalography and ophthalmoscopy remained normal. The nystagmus ceased at about the age of 2 years and one month. At the age of 3 years the strabismus was treated operatively.

Some motor and mental development have occurred but not to a satisfactory extent. The rudiments of speech could be discerned for a period, but these disappeared and absence of speech is now the dominating symptom. Some details of the course and the therapy are presented in Fig. 3.

Discussion

The favourable effect of therapy with thyroid hormone proves the presence of congenital myxedema. It appears also



Fig. 2. 9 months old. After 4 months of thyroid therapy.

certain that the child has, in addition, a toxoplasma infection as there is no justifiable ground to doubt the specificity of the serum reactions employed.

The weak complement-fixation reactions and the constant Sabin-Feldman reactions (dye-tests) in the mother are indications of a congenital infection in the child as the mother, in all probability, must have been infected before the birth of the child. The increase in the titre in the child must be regarded as significant as the individual values are reproduced and achieved with the same standard. The increase does not directly support the presumption of a congenital infection but its slow development is more suggestive

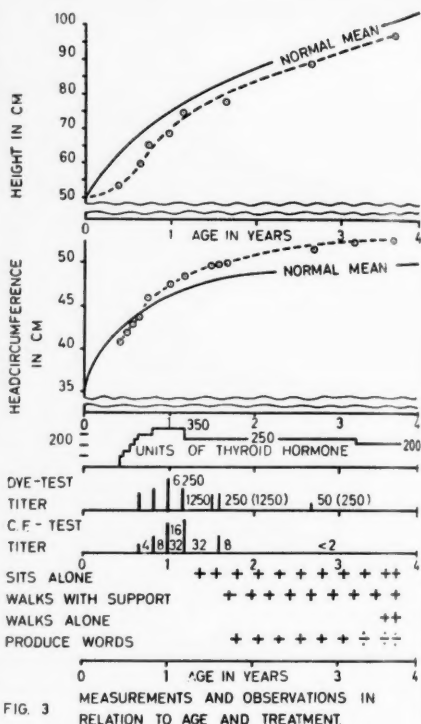


FIG. 3

of a congenital than an acquired infection. It is not known whether the ability to form antibodies is reduced in myxoedema but if this is the case, the increase in titre may be a sequel of therapy with thyroid hormone.

Congenital toxoplasmosis has been diagnosed *in vivo* in a considerable number of cases, particularly in the U.S.A.; but the serological investigations have apparently long been limited to children with chorioretinal changes (Sabin *et al.* (4)) and the question of the incidence of permanent positive serological reactions in infants with other symptoms or no symptoms still seems to be unanswered. The occurrence of clinically atypical, slight or entirely symp-

tomfree congenital toxoplasma infections cannot be excluded in advance as the cases found with the assistance of the ophthalmoscope vary considerably in the degree of severity (Feldman & Miller (3)). An isolated case of this nature has recently been recorded from the U.S.A. in which the child showed signs of encephalitis without intracerebral calcifications and chorio-retinitis shortly after birth. The toxoplasma infection demonstrated serologically has not yet had any effect on the subsequent development of the child (Stillerman 5).

In the present case, it must be supposed that the toxoplasma infection was responsible for the brief tendency to rigidity and opisthotonus, the nystagmus and the rapid increase in the circumference of the head at the commencement of the period of observation. It may become apparent in future whether the simultaneous occurrence of congenital myxoedema and congenital toxoplasmosis was only a coincidence. The simultaneous occurrence observed previously (Andersen (1)) and the rarity of the two conditions are evidence against this.

Summary

In an infant suffering from typical congenital myxoedema, thyroid hormone therapy was instituted at the age of 5 months. Thereafter nystagmus, strabismus, transient rigidity with a tendency to opisthotonus and striking increase in the circumference of the head gradually occurred. On account of these symptoms, when the child was 8 months old, serological investigations for toxoplasmosis on the mother and infant were undertaken. Positive reactions were found in both. An attempt is made to support the conception that, in addition to the congenital myxoedema, the infant suffers from a mild form of congenital toxoplasmosis. Finally, it is pointed out that this combination has been described once previously.

L'apparition simultanée de la toxoplasmose congénitale et du myxoedème congénital.

Chez un enfant atteint de myxoedème typique congénital, on a instauré à l'âge de 5 mois un traitement par l'hormone thyroïdienne. Depuis, on a observé graduellement l'apparition d'un nystagmus, d'un strabisme, d'une rigidité transitoire avec tendance vers opisthotonus et d'une augmentation frappante de la circonférence de la tête. A cause de ces symptômes, lorsque l'enfant fut âgé de 8 mois, on a fait des recherches sérologiques pour la toxoplasmose chez la mère et l'enfant. On a trouvé des réactions positives chez tous les deux. On a essayé de soutenir l'hypothèse qu'en plus du myxoedème congénital, l'enfant souffre d'une toxoplasmose congénitale, sous une forme faible. On a fait remarquer finalement que cette association a été décrite une fois auparavant.

Das gleichzeitige Zusammentreffen von angeborener Toxoplasmose und angeborenem Myxoedems.

Bei einem Säugling, der an typischem congenitalen Myxoedem litt, wurde im Alter von 5 Monaten Thyroid-Hormone-Therapie angewandt. Darauf traten Nystagmus, Strabismus, flüchtige Starrheit mit Tendenz zu Opisthotonus und auffallender Zunahme des Kopfumfanges fortschreitend auf. In anbetracht dieser Symptome wurden, als das Kind 8 Monate alt war, serologische Untersuchungen über Toxoplasmose bei der Mutter und dem Kinde angestellt. Bei beiden wurden positive Reaktionen gefunden. Es wird ein Versuch gemacht, den Begriff zu unterstützen, dass zusätzlich des angeborenen Myxoedems das Kind an einer milden Form von Toxoplasmose leidet. Endlich wird darauf hingewiesen, dass diese Kombination schon einmal früher beschrieben worden ist.

Aparición simultánea de toxoplasmosis congénita y mixedema congénito.

En un niño afecto de un típico mixedema congénito se instituyó a la edad de cinco meses tratamiento con hormona tiroidea. A partir de entonces apareció lentamente nistagmus, estrabismo, rigidez transitoria con tendencia al opistótonos y un notable aumento de la circunferencia del cráneo. Ante estos síntomas, y cuando el niño tenía ocho meses, se llevaron a cabo investigaciones serológicas para la toxoplasmosis en la madre y en el niño. Las reacciones fueron positivas en ambos. Se intenta apoyar el criterio de que además del mixedema congénito, el niño sufría una forma moderada de toxoplasmosis congénita. Finalmente se señala que esta asociación ha sido ya descrita anteriormente.

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Rigshospitalet
Copenhagen
Denmark

CASE REPORT

Successfully Treated Case of Cytomegalic Disease in a Newborn Infant

by H. H. VAN GELDEREN, M.D.

From the Pediatric Department of the University Hospital, Leyden, the Netherlands (Director Prof. G. M. H. Veeneklaas, M.D.)

Cytomegalia infantum (inclusion body disease, salivary gland virus disease) is not a new disease. The cells typical of the disease were first described by Ribbert in 1881, but they remained of interest only to pathologists for a long time. In the beginning various theories were evolved as to the nature of the cells, but these theories were completely speculative. About 1920 similar abnormalities were found in rodents, which were proved to be the result of a virus infection.

Since that time it has been generally accepted that the human form of the disease is also caused by a virus. This has recently been confirmed by Smith and Weller *et al.*, who isolated the virus from tissue and urine of cytomegalia-patients.

The disease was of little interest to the pediatrician until 1953, when the first diagnosis was established during life (Mercer *et al.*). A year earlier Fetterman had published a brief communication regarding a clinical diagnosis. Margileth described the first case of a patient who survived.

Various extensive review articles on cytomegalia infantum have been published,

i.a., by Farber *et al.*, Smith *et al.* and Wyatt *et al.*, while in 1957 Seifert & Oehme published a monograph which, in addition to a description of personal cases, contains a summary of the whole literature on this subject.

Only rarely does infection with the virus lead to manifest disease, as is also the case in animals. According to the autopsy results, in most of the cases only the salivary glands are involved, the typical giant cells with large nuclear and small cytoplasmatic inclusions being found at these sites (*first form*). Less often the typical cells are also found in other organs, in other words, a generalization (*second form*) is less frequently observed.

These two forms of the disease seem to have no clinical significance, because they are not attended by manifestations of disease in the patients. By far the majority of patients are infants, so that probably the infection occurs frequently, taking place at an early age.

Only when the infection occurs before birth does it lead to a clinically recognizable disease which, if not treated, is very likely to take a fatal course (*third form*). In rodents also the intra-uterine infection is the only form of contamination with cytomegalia virus which causes manifest disease.

Some authors (Seifert & Oehme; Wyatt

et al. c.s.) have tried to establish a relationship between the cytomegalia infection and the changes found at autopsy caused by the disease from which the child died. They described a great number of forms of cytomegalia, e.g., renal, intestinal, pulmonary and cerebral forms. It seems more probable, however, that cytomegalia is usually only a chance finding that has nothing to do with the fatal disease. Up to now we can only speak of cytomegalia as a disease as such when the infection has taken place in utero so that the child is already ill at birth.

The manifestations of this intra-uterine infection are typical. Directly after birth the children are icteric, they have an enlarged liver and spleen, thrombocytopenic purpura and erythroblastosis, a shift to the left of the neutrophils, and reticulocytosis. There are often also signs of cerebral damage such as microcephalia, hydrocephalia, calcification of the ventricular walls, and convulsions. The skeletal X-rays show the changes caused by prenatal damage: bright zones in the metaphyses and double contours in the tarsal nuclei (Seifert & Oehme). Hepatitis is also observed.

When the children are not treated most of them die after a period varying between some days and some weeks.

The diagnosis must be established by the demonstration of the typical giant cells, and also on the basis of the clinical picture. According to the literature, so far the diagnosis has been established during life only six times (Arey; Birdsong *et al.*; Guyton *et al.*; Haymaker *et al.*; Margileth; Mercer *et al.*); the typical cells were found in the urinary sediment, gastric washings and the CSF. Only two patients have been treated and remained alive (Birdsong *et al.*; Margileth).

The disease should first be differentiated from hemolytic disease of the newborn, as the two clinical pictures are very much alike. Blood group antagonism must therefore be excluded. Syphilis, toxoplasmosis, and other causes of icterus and thrombocytopenia must also be excluded. Bacterial sepsis neonatorum does not give rise to manifestations until some time after birth, unless parturi-

tion lasted long and the amniotic fluid was infected.

There is no causal therapy. Margileth and Birdsong *et al.* treated two patients successfully with cortisone and prednisone, respectively. These remedies were tried because of their effect on thrombocytopenia, hepatitis and hemolytic processes. Margileth also administered gammaglobulin, but to us there seems little reason for this when the patient has been infected in utero. The two patients mentioned seemed to be cured, apart from the sequelae of intracranial damage. It is not yet known whether the hepatitis heals without sequelae or whether it will eventually terminate in a cirrhosis.

We applied prednisone treatment in a patient with the congenital generalized form of cytomegalia in whom the diagnosis had been established shortly after birth, and we obtained a satisfactory cure.

The girl, A. L., was born on November 25th, 1957 after an uneventful partus. The mother had had a grippelike disease in the sixth month of gestation. The partus took place three weeks before term; the birth weight was about 2750 g. The patient was the seventh child. She had a marked purpura at birth. Respiration was irregular and she cried weakly. She was in bad condition on admission six hours post-natally; she had slight convulsions and a temperature of 33.3°C. Examination revealed, in addition to the purpura, a markedly enlarged liver and spleen, and icterus. The blood picture showed a leucocytosis (20,000/cu.mm), with 27 % immature granulocytes, erythroblastosis (11,800 nucleated red cells/cu.mm) and reticulocytosis (98 %).

Eighteen hours after birth serum bilirubin was 14.6 mg per 100 ml. The patient's blood group was A cde/cde, that of the mother A cDE/cde. The Coombs' test was negative.

When these data had become known a tentative diagnosis of cytomegalia infantum was accepted. In the course of the next days the following diseases were also excluded on

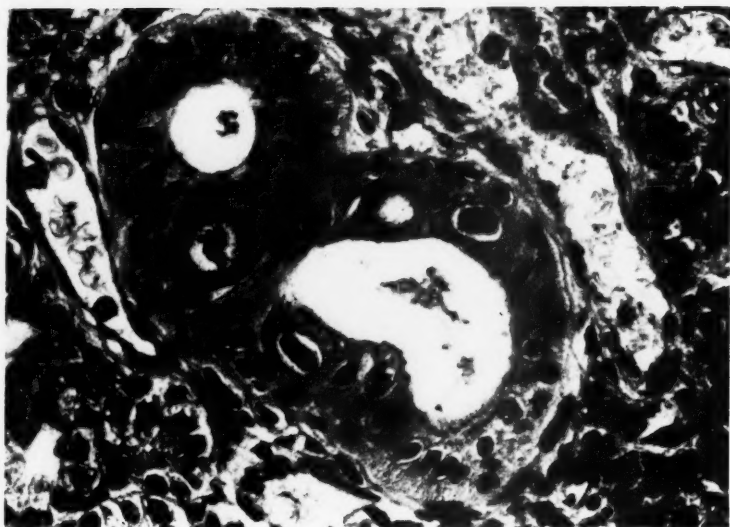


Fig. 1. Cytomegalia inclusion body cells in ducts of the parotis.

the basis of negative serological reactions: syphilis, toxoplasmosis, psittacosis.

Blood culture failed, but there was no evidence of bacterial sepsis. Blood diseases were excluded on the basis of normal mechanical and osmotic erythrocyte fragility, the absence of antibodies against erythrocytes and thrombocytes, and the bone marrow studies which only showed a shift to the left and active erythropoiesis. The CSF was normal, as was the EEG. The X-rays of the skull did not show calcifications; those of the thorax were normal. The X-rays of legs and feet showed radiolucencies in the metaphyses and double contours (Seifert & Oehme) in the tarsal nuclei. The urine did not contain glucose or galactose. Typical giant cells were never found in the sediment, but during the first weeks the very great number of tubular cells was a striking feature, corresponding with the findings in cytomegaly (Mercer *et al.*). Neither were giant cells found in bile or CSF. On one occasion a possible giant cell was found in the small amount of saliva that could be obtained from the patient.

Liver function was disturbed. Up to now no virus has been isolated from urine and faeces, but the search is going on.

Parotid biopsy was carried out on January 2nd, 1958. The gland contained numerous typical giant cells (Fig. 1 and 2). Skin biopsy failed to show giant cells in the sweat glands. Liver biopsy revealed, in addition to severe hepatitis with cholestasis and hematopoietic foci, structures which were regarded as degenerated cytomegalic cells (Fig. 3). We sent the biopsy specimen to Seifert, who confirmed the diagnosis of cytomegalia infantum.¹

We treated the patient with prednisone for three months. During the first few days she was also given vitamin K, phenobarbital, penicillin and streptomycin.

The child remained very ill during the first two weeks, and there was sclerodema for some days. Subsequently she recovered rapidly, however. The purpura cleared up after two to three weeks, but the icterus had not disappeared completely until after three months. At the time of writing liver and

¹ A more extensive description of the pathology will be published elsewhere by van Gelderen and de Man.

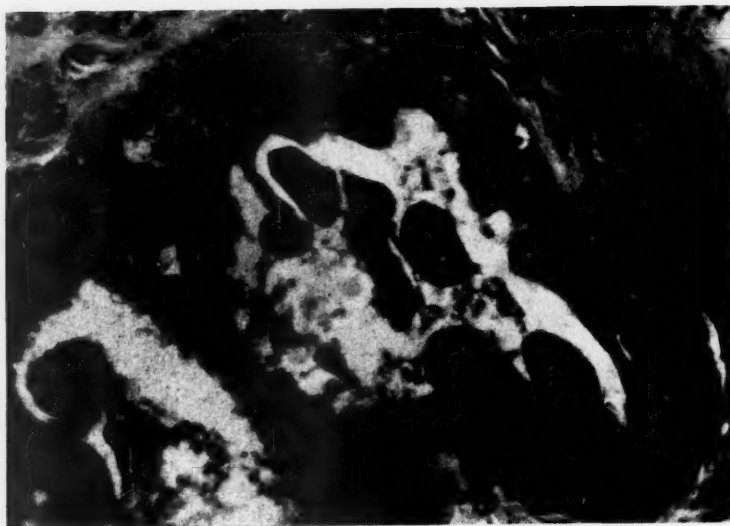


Fig. 2. Several large cytomegalia cells in the lumen of a parotis-duct.



Fig. 3. Degenerated cytomegalia-cell in liver.

spleen are not enlarged. The hematological abnormalities had disappeared after two months. The child gained weight and length at a normal speed and development is quite normal. Signs of cerebral damage have never been observed, apart from the mild convulsions in the first days of life.

At present, 13 months after birth, the child is completely healthy.

Discussion

The patient described above is the seventh case of congenital generalized cytomegalia infantum described in the literature in whom the diagnosis was established during life, and the third which has remained alive with treatment and is probably cured. The diagnosis was confirmed by means of biopsies. The demonstration of cytomegaly in the parotid gland is not quite sufficient for the diagnosis; generalization must also be proved. The clinical picture is, however, of great diagnostic importance. Cortisone treatment should be started very early, as soon as the disease is suspected (after differentiation from hemolytic disease of the newborn), in view of the high mortality during the first few weeks.

The diagnosis can be clinched early when giant cells are found in the urinary sediment or other body fluids, but this is not always the case. Then, as long as thrombocytopenia does not allow biopsies, we shall have to be satisfied with a diagnosis per exclusionem.

When one has a laboratory at one's disposal where the virus can be isolated from urine and where neutralizing antibodies can be demonstrated, there is a possibility of a positive outcome about eight weeks after birth. In this case biopsies are probably not necessary. A parotid biopsy is a minor procedure; when no giant cells are found in this gland, cytomegalia is very unlikely. Conversely, the demonstration of giant cells in the parotid gland is no proof that the child suffers from generalized cytomegalia, because these cells have been found in the salivary glands of numerous infants in many regions. As far as we know, however, the congenital form of the disease with its typical clinical picture has never been found with parotid involvement only; it seems very likely therefore that demonstration of parotid cytomegalia in *typical* cases is sufficient for the diagnosis.

Summary

Description of a girl with congenital generalized cytomegalia infantum. The diagnosis was based on the clinical picture, and was confirmed by parotid and liver biopsies. The child recovered following prednisone treatment. This is the seventh case diagnosed during life and the third treated successfully.

Cytomegalia infantum is a virus disease which probably only leads to a clinically recognizable disease after intra-uterine infection. Early recognition is possible and also necessary, because the prognosis is gloomy when no treatment is instituted.

Un cas de cytomegalia infantum traité avec succès.

Description d'une fille avec un cytomegalia infantum congénital généralisé. Le diagnostic était basé sur le tableau clinique et confirmé par des biopsies de la parotide et du foie. L'enfant s'est

rétablie à la suite d'un traitement à la prednisone. Ceci est le septième cas diagnostiqué lorsque le malade est encore en vie et le troisième où le traitement a réussi. Le cytomegalia infantum est une maladie à virus qui mène probablement à une affection cliniquement décelable seulement après une infection intra-utérine. Une identification précoce est possible et nécessaire aussi car le pronostic est triste si aucun traitement n'est instauré.

Ein erfolgreich behandelter Fall von Cytomegalia infantum.

Beschreibung eines Mädchens mit angeborener allgemeiner Cytomegalie. Die Diagnose wurde auf grund des klinischen Bildes gestellt und wurde durch Biopsie der Parotis und der Leber befestigt. Das Kind genas nach angestellter Behandlung mit Prednison. Das ist der siebente Fall, der während des Lebens, der diagnostiziert wurde und der dritte mit Erfolg behandelt wurde. Cytomegalia infantum ist eine Viruskrankheit, welche wahrscheinlich nur zu einer klinisch erkennbaren Krankheit nach intra-uteriner Infektion führt. Frühzeitige Erkennung ist möglich und auch notwendig, weil die Prognose trübe ist, wenn keine Behandlung vorgenommen wird.

Un caso de citomegalia infantil tratada con éxito.

Se describe el caso de una niña afecta de una citomegalia infantil congénita generalizada. El diagnóstico se estableció por el cuadro clínico y fue confirmado por las biopsias de parótida e hígado. El niño se recuperó después del tratamiento con prednisona. Es este el séptimo caso diagnosticado durante la vida y el tercero tratado con éxito. La citomegalia infantil es una enfermedad vírica que probablemente solo da lugar a una enfermedad reconocible clínicamente después de la infección intrauterina. Su conocimiento precoz es posible y también necesario, puesto que el pronóstico es sombrío cuando no se instituye tratamiento.

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Pediatric Department
University Hospital
Leyden
The Netherlands

PROGRESS IN PEDIATRICS

Twenty-one Cases of Anterior and Posterior Diaphragmatic Hernias in Children

by J. LESTER, J. VESTERDAL and C. C. WINKEL SMITH

From the University Clinic of Radiology (Head: Prof. G. Thomsen, M.D.) and the University Clinic of Pediatrics (Head: Prof. P. Plum, M.D., Children's Surgeon: C. C. Winkel Smith, M.D.), Copenhagen

The present study comprises 21 cases of diaphragmatic hernia in children below 4 years of age admitted to the University Clinic of Pediatrics, Rigshospitalet, Copenhagen, during the years 1945–56. This series includes only hernias through the anterior or posterior part of the diaphragm. The cases of hiatus hernia admitted in the same period have been published by Engberg, Thomsen & Vesterdal (1957).

The congenital diaphragmatic hernia is not so rare as previously assumed. In many cases prompt surgical intervention is life-saving, and it is therefore of great importance that all cases suspect of diaphragmatic hernia are examined radiologically, and that both the pediatrician and the radiologist know the characteristic features of this condition.

Embryology and Anatomy

We shall briefly review the embryology of the diaphragm, as some knowledge of this is necessary to understand how the hernias arise.

The diaphragm is developed through fusion of four parts: a ventral, a dorsal, and a right and left lateral. The ventral part is

developed from the septum transversum. The posterior part of this septum fuses with parts of the dorsal mesentery so that a bridge is formed over the coelom cavity. On each side is in this way formed the pleuroperitoneal canal which in the third fetal month is closed by an ingrowth (the third or fourth component of the diaphragm) from the lateral chest wall which joins the above-mentioned parts of the diaphragm. Thus, the development of the diaphragm is rather complicated, and it is no wonder that congenital defects are not infrequently met with.

The posterior diaphragmatic hernias protrude between the lumbar and the costal parts of the diaphragm where there is a weak area called the lumbocostal triangle. This was first described by Bochdalek (1848) and hence hernias here are named Bochdalek hernias. In 90 per cent of these hernias no hernial sac is present because they have arisen before the pleuroperitoneal canal was closed. The remaining 10 per cent have originated later, but before the muscle fibres have grown into the lumbocostal triangle, and they therefore have a hernial sac. The Bochdalek hernias are 3 to 4 times more frequent on the left side than on the right, because the liver protects the weak area on the right side.

The anterior hernias protrude between the costal and the sternal fibres of the dia-

phragm where a weak area is found on each side (Larrey's cleft). Hernias through this were first described by Morgagni (1769), hence the name Morgagni hernias. These almost always have a hernial sac.

In their classification of the diaphragmatic hernias, Ladd & Gross (1941) include only Bochdalek and Morgagni hernias and hiatus hernias, while other authors also include congenital absence of one half of the diaphragm or of the central tendon. The two latter anomalies do not occur in our series. Hernias through the hiatus aortae or the hiatus venae cavae have never been observed.

Case Material

This series (Table 1) comprises 21 children with diaphragmatic hernia, 11 boys and 10 girls, aged 18 hours—3½ years. The average age for all the children was 11.7 months, for the children with Morgagni

hernias 14.5 months and for those with Bochdalek hernias 8 months. In the same period (1945–56) 63 children (average age 31 months) were admitted on account of hiatus hernia.

In our series, 12 cases had anterior (Morgagni) hernias and 9 posterior (Bochdalek) hernias.

Only two had right-sided hernias, and these were both anterior. Nineteen cases had left-sided hernias, half of these being anterior and half posterior. A hernial sac was present in all cases of Morgagni hernia, but only in one third of the cases of Bochdalek hernias. The size of the hernias varied considerably. From one third to all of the pleural cavity concerned might be filled with the intestinal loops. The hernias without a sac were very large (at least ½ of the pleural cavity).



Fig. 1.



Fig. 2.

Figs. 1 and 2. Seven weeks old girl with a great Bochdalek hernia. The intestinal loops reach the top of the left pleural cavity, and the heart is displaced far to the right. On the lateral radiogram it is seen that the defect is in the posterior part of the diaphragm (Case 9).

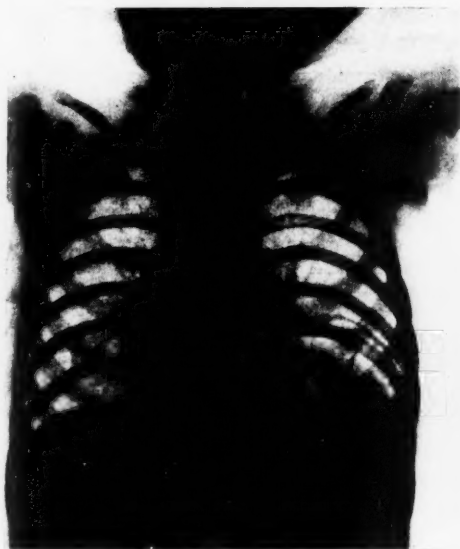


Fig. 3.



Fig. 4.

Figs. 3 and 4. Sixteen months old girl with a Morgagni hernia which contains the stomach and colon. The heart is moderately displaced to the right. The defect in the diaphragm is in its anterior part (Case 8).

The symptoms which the children presented were dependent on the size of the hernia and not on the localization. Twelve of the children had dyspnoea and/or cyanosis, and 4 had recurrent attacks of pneumonia; these symptoms were most pronounced in the youngest infants. Some of these cases had, in addition, abdominal symptoms, particularly vomiting and bad thriving. Four children had only abdominal symptoms. In one case, a girl aged 2½ years, no symptoms at all were present, and the hernia was detected at tuberculosis control.

Four cases had other congenital anomalies: 2 had malrotation of the intestine, 1 situs inversus thoracis and 1 omphalocele and atrial septal defect.

The diagnosis was easy in the typical cases (Figs. 1-4). In a few cases, however, it was difficult. In one case a congenital cystic lung was diagnosed at the first examination, but new radiograms taken in different projections permitted the correct diagnosis. Another child had a large Morgagni hernia into the pericardium (Thomsen, Vesterdal & Winkel Smith, 1954); this case presented great diagnostic difficulties because this clinical picture was little known, but by review of the preoperative radiograms it was found that it would have been possible to make the correct diagnosis preoperatively. Three cases were first considered to have a relaxation of the diaphragm, but on operation a Morgagni hernia was found in all

TABLE 1. *Twenty-one cases of diaphragmatic hernia.*

Diaphragmatic hernia											
Case no.	Sex	Age	Type	Side	Size ^a	Hernial sac	Chief symptoms ^b	Operation	Re- sult	Observation time	
1.	375/45 F	15 mos.	post.	L	$\frac{1}{2}$	+	(?)	V.B.	none	died	4 yrs. after operation
2.	565/45 F	3 yrs.	ant.	R	$\frac{1}{2}$	+		D.C.	abd.	died	at operation
3.	996/47 M	6 wks.	post.	L	1	-		D.C.P.	abd., 2-stage	cured	10 yrs.
4.	1006/47 M	3 wks.	ant.	L	$\frac{1}{2}$	+		D.	abd., 2-stage	died	5 d. after operation
5.	234/48 F	1 day	post.	L	1	-		D.C.	abd., 2-stage	died	1 d. after operation
6.	649/49 F	1 day	ant.	L	$\frac{1}{2}$	+		D.C.	none	died	53 days old
7.	769/49 M	2 yrs.	ant.	L	$\frac{1}{2}$	+		D.P.	abd.	cured	7 yrs. ^c
8.	94/50 F	16 mos.	ant.	L	$\frac{1}{2}$	+		B.P.	abd.	cured	7 yrs.
9.	612/51 F	7 wks.	post.	L	1	-		V.	abd.	cured	6 yrs.
10.	911/51 M	5 mos.	post.	L	$\frac{1}{2}$	+		B.	thorac.	cured	6 yrs.
11.	139/52 M	15 mos.	ant.	R	$\frac{1}{2}$	+		P.	abd.	cured	6 yrs.
12.	392/52 M	6 wks.	ant.	L	$\frac{1}{2}$	+		V.B.	abd.	cured	5 yrs.
13.	683/53 M	2 mos.	post.	L	$\frac{1}{2}$	-		D.C.	thor.-abd.	cured	1 yr.
14.	1101/53 F	2 yrs.	ant.	L	$\frac{1}{2}$	+		P.	thorac.	cured	3 yrs.
15.	795/54 M	4 wks.	post.	L	$\frac{1}{2}$	+		C.	abd.	cured	2 yrs.
16.	1015/54 M	6 wks.	ant. ^d	L	$\frac{1}{2}$	+		C.V.	abd.+thor.abd.	cured	$\frac{1}{2}$ yr.
17.	153/55 F	2 wks.	ant.	L	$\frac{1}{2}$	+		C.	thorac.	cured	2 yrs.
18.	610/56 F	2 yrs.	ant.	L	$\frac{1}{2}$	+		None	thorac.	cured	1 yr.
19.	845/56 M	7 mos.	post.	L	$\frac{1}{2}$	-		D.	thor.-abd.	cured	10 mos.
20.	1009/56 F	3 yrs.	post.	L	$\frac{1}{2}$	+		V.B.	thorac.	cured	6 mos. ^c
21.	1161/56 M	4 mos.	ant.	L	$\frac{1}{2}$	+		D.C.	abd.	cured	6 mos.

^a Size in comparison with pleural cavity.^b B.: bad thriving, C: cyanosis, D: dyspnoea, P: recurrent pneumonia, V: vomiting.^c Information by parents, no radiogram.^d Into pericardium.

three cases, and by review of the preoperative radiograms it was found that the correct preoperative diagnosis could have been possible. In the remaining cases the preoperative radiological diagnosis was correct.

Treatment.

Two patients were not operated upon, and they both died. One of these had a large omphalocele which was operated the day after birth. The infant died 53 days later without having been operated upon

for the diaphragmatic hernia; in addition he had an atrial septal defect. In the other non-operated case a Bochdalek hernia was diagnosed in 1945, but at that time the attitude towards surgical treatment was not very active, and operation was postponed and the child discharged. He died later at the age of 2 years, the cause of death being unknown.

Nineteen of the cases were operated upon, 5 through a thoracotomy, 2 by a combined thoraco-abdominal operation

and 11 through a laparotomy. In 3 of the last mentioned cases the closing of the abdominal wall was so difficult that the two-stage method of Gross had to be employed. One of these infants survived and the two others died (these were not anesthetized with intubation). In the 19th case operated upon, the child with the Morgagni hernia into the pericardium, an abdominal and later a thoraco-abdominal operation were done.

Results of treatment.

As mentioned before, the two non-operated children died. Of the 19 operated children, 4 died. Three of these died at the operation or in the postoperative period, and these three deaths all occurred in or before 1948, at which time intubation anesthesia was introduced at this Hospital. Two of these were very young infants. The fourth fatal case was a 6-weeks-old infant who was extremely emaciated.

In the remaining 15 cases (79 per cent) the operation and postoperative course were without complications. Radiograms taken when the children were discharged were normal in all cases. Thirteen of these children have been seen for follow-up examination later (observation time $\frac{1}{2}$ –10 years), and they were all well and had normal chest radiograms. In the two remaining cases the parents have informed us that the children are without any symptoms.

Discussion

The first case of congenital diaphragmatic hernia was reported in 1698 by Riverius, but even earlier the traumatic diaphragmatic hernia was described (Am-

broise Paré, 1575). J. L. Petit (1674–1750) was the first to make a clear distinction between diaphragmatic hernia and relaxation of the diaphragm, and he ascribed the more frequent occurrence of left-sided diaphragmatic hernias to the presence of the liver on the right side.

Innumerable publications on diaphragmatic hernia have since appeared, but very few deal with this condition in infancy and early childhood. In this period of life the symptoms, prognosis and indications for operation are different from those in adults, as particularly Truesdale (1936) has pointed out.

Also in Scandinavia a number of papers on diaphragmatic hernia have been published, but only three deal with hernias in children. Hertz (1890) reports 8 cases of diaphragmatic hernia found post-mortem in infants who died within two hours after birth, and he reviews the subject well and extensively. Johansen (1932) has reported a case of right-sided diaphragmatic hernia in a one-year-old boy, and Thomsen, Vesterdal & Winkel Smith (1954) have published the case of Morgagni hernia into the pericardium that is mentioned above in our series.

As pointed out by Haugen & Ehrenberg (1942), the frequency of diaphragmatic hernia is considerably greater in the reports based on autopsy than in those based on clinical experience. This seems to indicate that many infants with this defect die immediately after birth, before the clinical diagnosis has been made.

The *symptoms* differ in the different age groups. In the newborn, the symptoms are mainly thoracic, such as cyanosis and dyspnoea. In our series, 8 of the 10 infants below two months of age had dyspnoea or

cyanosis, while only 4 of the 11 children older than two months had these symptoms. The cyanosis may be permanent or occur in attacks provoked by crying or feeding. The cyanosis may disappear when the child is placed on the side on which the hernia is located; in this position the mediastinum sinks towards the diseased side, and thus a better aeration of the upper lung is permitted (Ladd & Gross, 1941).

In somewhat older children the main symptoms are vomiting, particularly immediately after meals, and bad thriving. In addition, recurrent attacks of pneumonia are often seen. In some cases the clinical picture may be confusing, owing to the presence of other congenital anomalies, particularly malrotation of the intestine or, less frequently, congenital malformations of the heart, cleft palate, Klippel-Feil's syndrome or omphalocele. In most cases, however, the diaphragmatic hernia is the only defect, and Potter (1952) holds the view that it is one of the congenital defects which most often occur as an isolated anomaly.

The *physical signs* are most conspicuous in the newborn. In addition to dyspnoea and cyanosis, a sunken abdomen will be found when a great part of the intestines are displaced into the thoracic cavity. Intestinal gurgling may be heard over the thorax, and the heart may be displaced.

A child with the above mentioned physical signs is highly suspect of having a diaphragmatic hernia, but a positive diagnosis is only possible by radiological examination.

Radiological findings.—A plain frontal radiogram will show that one half of the thorax is more or less filled with the hernia,

and the lung is correspondingly compressed. The heart and the trachea may be displaced towards the other side with subsequent compression of the other lung. Morgagni hernias may also dislocate the heart backwards. In our series, 19 cases had displacement of the heart. The size and position of the defect in the diaphragm are generally best estimated on a lateral radiogram. Whether a hernial sac is present or not is as a rule also best judged from a lateral radiogram: if the intestinal loops are seen localized in a smaller part of one thoracic cavity, a hernial sac generally is found. If, on the other hand, the intestinal loops fill the whole thoracic cavity to the top, it is rare that a hernial sac is present (Gross, 1953). Frequently one is inclined to believe that one half of the diaphragm is totally absent, but this condition is extremely rare, and generally, when the radiogram is carefully scrutinized, the remaining part of the diaphragm will be seen as a shelf which may be pressed down by the overlying intestinal loops (Marks, 1953).

In infants the diagnosis ought to be made solely on the basis of plain radiograms. It is inadvisable to give a barium meal because of the risk of aspiration pneumonia or obstruction of the small intestine (Ladd & Gross, 1941). Moreover, it is of minor importance to know which organs are displaced into the thorax, as the patient in any case ought to be operated as soon as possible.

To older children a small barium meal, preferably of rather fluid consistency, may be given without risk. In this age group Morgagni hernia is the more frequent type, and in such cases a barium meal is often necessary, as the diagnosis may be difficult

owing to the small size of the hernia or overlapping by the heart shadow (Ritvo & Petterson, 1944).

Differential diagnosis.—Diaphragmatic hernia may be mistaken for various lung diseases, particularly lung cysts. This happened in one of our cases. It should, however, be possible to make the correct diagnosis by careful study of the radiograms.

It is often difficult or even impossible to distinguish between diaphragmatic hernia and relaxation of the diaphragm. In the latter condition, which is rare in children, the elevation of the diaphragm is due to aplasia of the muscle fibres. It occurs most often on the left side. The heart may be dislocated, but generally the lung is not compressed. Schintz (1951) states that a great variation of the upper limit of the hernia from day to day, or when the position of the child shifts from lying to standing, indicates that it is a hernia and not a relaxation. It is, however, difficult to ascertain such changes in children, and it is therefore often impossible to distinguish preoperatively between these two conditions. In three of our cases we had this difficulty.

Treatment.—In the newborn infant a large diaphragmatic hernia is a very dangerous disease. It is very important that the child is treated surgically as soon as the diagnosis is made, if possible immediately after birth or in the first days of life. At this time the procedure is facilitated by the emptiness and incomplete distension of the intestines, and, moreover, the resistance of the infant to surgery seems to be greater in the newborn period than when the infant is some weeks old.

With regard to the operative technique one has to choose between the abdominal and the thoracic approach. If the hernia is very large and the infant very young, most surgeons nowadays will prefer the abdominal approach. This seems to be with good reason, as reposition of the abdominal contents frequently is quite impossible from the pleural cavity alone, and because the abdominal approach permits a general inspection of the intestines, so that a malrotation, if present, may be detected. In the most severe cases operated through laparotomy, the operation may be done in two stages (Gross): in the first stage the abdominal wall is closed, after reposition of the hernia, by suturing the skin alone, so that undue stress on the diaphragm is avoided; in the second stage, which takes place after some days or weeks, all the layers of the abdominal wall are sutured in the usual anatomical correct way.

In older children and in cases where the hernia is small the transthoracic approach is without doubt the preferable method, as it is the easiest way to make a reposition of the hernia and a sufficiently solid closing of the defect in the diaphragm.

In our series the number of patients is too small to permit reliable conclusions with regard to the surgical procedure, but we feel, in accordance with previous authors, that the abdominal approach is preferable in early infancy, while the thoracic approach is easier when the child is more than 10–12 months old.

Prognosis.—Hedblom (1925) reported a series of 22 operated children below 10 years of age (20 cases collected from the literature and two cases of his own). Nine of these were fatal (41 per cent).

In the following years adequate treatment has improved the prognosis, and in 1955, Gross reported a mortality of 11 per cent in his series of 71 operated cases.

In our series the over-all mortality of

the operated cases is 21 per cent. However, the cases operated after 1948 when intubation anesthesia was introduced had a mortality of only 6 per cent.

Summary

Diaphragmatic hernia is not very rare. It is a dangerous condition which untreated has a high mortality. The diagnosis must be kept in mind both in cases with thoracic symptoms and in cases with abdominal symptoms. Diaphragmatic hernia may be mistaken for lung diseases. The treatment is surgical, and the operation must be done as soon as the diagnosis is made, if possible immediately after birth.

The authors report a series of 21 children with diaphragmatic hernia, 12 with Morgagni hernia and 9 with Bochdalek hernia. Two cases died without being operated upon. Of the 19 operated cases 4 died. However, 3 of these deaths occurred before 1948 when intubation anesthesia was introduced, and after 1948 the mortality was only 6 per cent.

Hernie diaphragmatique chez les enfants. 21 cas de hernie de Bochdalek ou de Morgagni.

L'hernie diaphragmatique n'est pas une maladie très rare. C'est une maladie dangereuse avec une mortalité élevée si elle n'est pas traitée. On doit penser à ce diagnostic dans des cas avec des symptômes thoraciques aussi bien que dans ceux avec des symptômes abdominaux. L'hernie diaphragmatique peut être prise à tort pour une maladie pulmonaire. Le traitement est chirurgical, et l'opération doit être effectuée dès que le diagnostic est posé et, si possible, aussitôt après la naissance.

Les auteurs rapportent une série de 21 enfants avec une hernie diaphragmatique, 12 avec une hernie de Morgagni et 9 avec une hernie de Bochdalek. Deux cas sont morts, sans en avoir été opérés. Des 19 cas opérés, il y eut 4 décès. 3 de ces cas décédèrent cependant avant 1948 lorsqu'une anesthésie par intubation fût introduite. Après 1948, la mortalité ne s'éleva qu'à 6 %.

Zwerchfellhernien bei Kindern. 21 Fälle von Bochdalek oder Morgagni-Hernie.

Zwerchfellhernie ist nicht sehr selten. Es ist ein gefährlicher Zustand, der unbehandelt eine hohe Sterblichkeit zur Folge hat. An diese Diagnose muss man sowohl in Fällen mit thorakalen Symptomen wie auch in Fällen mit abdominalen Symptomen denken. Eine Zwerchfellhernie kann man irrtümlicherweise für Erkrankungen der Lunge ansehen.

Die Behandlung ist chirurgisch, und die Operation soll, sobald die Diagnose festgestellt ist, frühzeitig ausgeführt werden, wenn möglich direkt nach der Geburt.

Die Autoren referieren eine Serie von 21 Kindern mit Diaphragma-Hernie (H. diaphragmaticae), 12 mit Morgagni-Hernie und 9 mit Bochdalek-Hernie. Zwei Fälle kamen ad exitum ohne vorher operiert zu sein.

Von 19 operierten Fällen starben 4.

Drei dieser Todesfälle ereigneten sich vor 1948, nach Einführung der Intubationsnarkose (1948) betrug die Mortalität nur noch 6 %.

Hernia diafragmática en el niño. 21 casos de hernia de Bochdalek o de Morgagni.

La hernia diafragmática no es demasiado rara. Es una enfermedad peligrosa cuya mortalidad es muy elevada si no se instituye tratamiento. Hay que pensar en la posibilidad de su diagnóstico tanto en los casos con síntomas torácicos como en los que cursan con manifestaciones abdominales. La

hernia diafragmática puede confundirse con procesos pulmonares. El tratamiento es quirúrgico y la intervención debe ser llevada a cabo una vez establecido el diagnóstico, a ser posible inmediatamente después del nacimiento.

Los autores presentan una serie de 21 niños con hernia diafragmática, 12 con hernia de Morgagni y 9 con hernia de Bochdalek. Dos casos fallecieron antes de ser operados. De los 19 operados murieron 4. No obstante 3 de estos fallecimientos ocurrieron antes de 1948, en que comenzó a emplearse la anestesia por intubación; con posterioridad a 1948 la mortalidad fue solamente del 6 por ciento.

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(J.V.). Børneafdelingen
Rigshospitalet
Kopenhagen Ø
Denmark

PROGRESS IN PEDIATRICS

A Follow-up Study of 514 Children of Diabetic Mothers

by L. HAGBARD, I. OLOW and T. REINAND

From the Department of Obstetrics and Gynecology (Professor Herbert Fredrikson, deceased), and the Department of Pediatrics (Acting Professor B. Lindquist)

Since the beginning of insulin therapy for diabetes mellitus, women with this disease have become practically as fertile as other women. More and more diabetic women have become pregnant during recent years and more and more is being learned about the course of a diabetic pregnancy. The mothers now run a relatively slight risk when their case is properly handled, but they still lose a great many of their babies. A large amount of work and research has been done to try to find ways of cutting down the infant losses, and the results have also improved greatly in many places, particularly during the last ten years. The reader is referred to the publication of one of us (Hagbard) in 1956 for an extensive review of the literature in this field.

Thus, most of the recent research on diabetic pregnancies has been devoted to ways of reducing the perinatal mortality. Not much attention, however, has been paid to the outcome of the children surviving the neonatal period. This is undoubtedly because hitherto it has not been possible to obtain a large enough series which has been observed for a long enough time. Only a few reports are forthcoming on the long-term

prognosis of the children of diabetic mothers. One of the first Scandinavian reports on this matter was by Stendahl (1952) who re-examined 58 children of diabetic mothers. In his opinion, the prognosis was good for the children who survived the first year. Pedersen & Schondel (1949) found from a study of 91 children that the prognosis was fairly good for children who survived the neonatal period.

We made the same observations in a study published together with Fredrikson in 1957 of 123 children of diabetic mothers. This study included a complete pediatric examination by two of us (Olow and Reinand), covering the children's physical and mental development. In addition to the ordinary physical examination, we measured the height and weight of the children, and whenever there was reason we also took roentgenograms, electrocardiograms and phonocardiograms. We found diabetes in only one of the children, then aged 20. We gave 87 children 5 years old and older a glucose tolerance test. None of the glucose tolerance curves were distinctly abnormal, all the two-hour values being normal. In 10 cases, however, the maximum blood sugar value lay between 200 and 230 mg per hundred ml of blood. We found one deformity,—congenital heart disease with a defective interventricular septum in a one year old boy. These were the only abnormalities, physical and mental, we found in these children. Thus 121

out of the 123 children were quite normal at the time they were re-examined. The average age of the children was 14 years. The average age of the 82 children born before the onset of the diabetes in the mother was 19 years and that of the 41 children born after the onset of the diabetes 6 years.

Thus, judging by the Scandinavian research hitherto, children born of diabetic mothers have a favourable long-term prognosis. Comparatively few cases have been studied, however, and many of them have been observed for too short a time. As we are of the opinion that the long-term prognosis for these children is a question of great clinical significance, we shall now report our observations in a follow-up study of a larger series.

Present Series

Collection and treatment of data

In 1956 one of us (Hagbard) published a study of 467 pregnancies in 366 diabetic mothers delivered at 21 obstetric departments in different parts of Sweden, and in 1958 a similar study of the same mothers' pregnancies before they got their diabetes. Both these studies only took up the complications and mortality in the children during the perinatal period.

The present study takes up the outcome of the 366 mothers' 611 children who survived the neonatal period, which in Sweden is limited to the first seven days after birth. Two hundred and fifteen of these 611 were born before the onset of the diabetes in the mother and 396 after.

The mothers were sent a questionnaire where they were asked to give the height and weight of their children and their state of health at the time. They were also asked to fill out whether the children had had any serious diseases, whether they had received medical care or had been admitted to a hospital and the name of the children's

welfare center to which they had gone. They were also asked to state whether the children had shown any disorders in development, difficulties at school and the like. Whenever there was any reason to do so, information was requested from physicians attending the children or children's welfare centers and excerpts from the records were requested from hospitals.

Since most Swedish mothers go to the children's welfare center, we were able to get satisfactory data about 514 children. Whenever no information was obtainable, it was because the family had broken up or moved and could not be traced.

Composition of series

The follow-up series consists of 164 children born before and 350 born after the mother's diabetes was detected (Table 1).

The age distribution of the children at the time of the follow-up study is seen from Table 2 and Fig. 1. As appears there, 73 per cent of the children were younger than 11 years at the time the questionnaire was filled out and 27 per cent were older. The children born after the mother got her diabetes were naturally younger than the ones born before. As seen from Table 2, only 6 per cent of the ones born after were 11 years old or older at the time of the follow-up study, as opposed to 72 per cent of the ones born before the onset of the maternal dia-

TABLE 1. *Present series of children of diabetic mothers.*

Number of babies	Born before onset of diabetes in mother	Born after onset of diabetes in mother	Total
Surviving beyond first week	215	396	611
Data for follow-up study lacking	51	46	97
Included in follow-up study	164	350	514

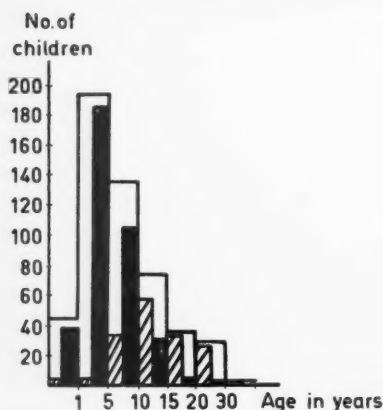


Fig. 1. Age distribution of children at time of follow-up, the obliquely lined columns representing the babies born before the onset of the mother's diabetes and the black columns the babies born after the onset of the mother's diabetes.

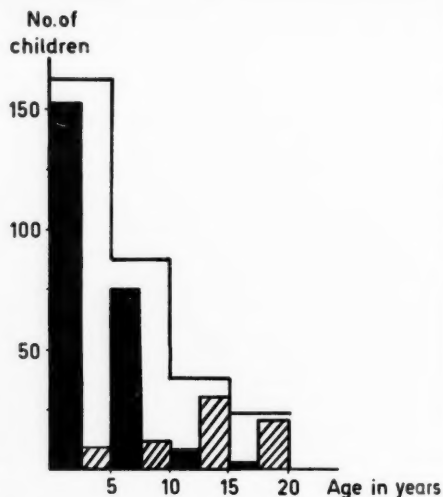


Fig. 2. Age distribution at time of follow-up of the 307 children examined for height and weight, the obliquely lined columns representing the babies born before the onset of the mother's diabetes and the black columns the babies born after the onset of the mother's diabetes.

TABLE 2. *Age of children at time of follow-up study.*

The figures in brackets denote the number of dead children.

Age in years	Babies born before onset of mother's diabetes		Babies born after onset of mother's diabetes		Total	
	No.	%	No.	%	No.	%
- 1	6 (6)	3.7	39 (16)	11.1	45 (22)	8.8
1- 5	6 (1)	3.7	186 (2)	53.1	192 (3)	37.4
6-10	34	20.7	104	29.7	138	26.8
11-15	58 (1)	35.4	15	4.3	73 (1)	14.2
16-20	31	18.9	4	1.1	35	6.8
21-30	27	16.5	2	0.7	29	5.6
> 30	2	1.1	—	—	2	0.4
Total	164 (8)	100.0	350 (18)	100.0	514 (26)	100.0

betes. The average age was 5 and 15 years, respectively, for the two groups and 8 years for the whole series.

Results

Before going into details, it will be pointed out that 332, or 94.9 per cent, of the 350 children whose mothers had full-blown diabetes and who survived the neonatal period were living at the time of the

follow-up. Of these 323, or 92.3 per cent of all 350 children, were healthy and normal. A review of these cases is given in Table 3.

It was hard to get sufficient data about all the children born before the mother got diabetes, and so it is not possible to give the corresponding figures for these children.

TABLE 3. *Outcome of the 350 children born after onset of diabetes in mother and surviving the first week of life.*

Age in years	No. of babies surviving first week of life	No. of babies dying later	Children alive at time of follow-up		Healthy children at time of follow-up	
			No.	%	No.	%
< 1	39	16	23	59.0	22	56.4
1- 5	186	2	184	98.9	180	96.8
6-10	104	—	104	100.0	102	98.1
11-15	15	—	15	(100.0)	13	(86.7)
16-20	4	—	4	(100.0)	4	(100.0)
21-30	2	—	2	(100.0)	2	(100.0)
Total	350	18	332	94.9	323	92.3

Mortality

Eighteen, or 5.1 per cent, of the 350 children born after their mother got diabetes, had died, while 8, or 4.9 per cent of the 164 children born before their mother got diabetes, had died. Practically all the deaths in both groups occurred in the first year of life. There was no difference in the mortality in the two groups.

Table 4 shows the ages of the 26 children when they died. Twenty-two of them died before they became a year old and half of these before they had lived one month.

The causes of death are shown in Table 5. As seen there, malformation was a frequent cause. Thus in 6 cases the death

could be ascribed wholly to malformation, —in 4 cases to deformity of the cardiac vessels, in 1 case to severe cerebral deformity, and in 1 case to urethral stricture leading to bilateral hydronephrosis and uremia. In 3 other cases malformation contributed greatly to the fatal outcome, though the immediate cause of death was infection.

Most of the deaths, or 10 of them, were caused by infection. In many of these cases immaturity or malformation contributed to the death. It is worthy of note that all the children who died of an infection did so during their first year and 7 during their first month.

TABLE 4. Age at death of the 26 children who died.

	Died during first month		Died within two months		Died during 1st year of life		Total	
	No.	%	No.	%	No.	%	No.	%
Babies born before onset of mother's diabetes (164 babies)	2	1.2	4	2.4	6	3.7	8	4.9
Babies born after onset of mother's diabetes (350 babies)	11	3.1	13	3.7	16	4.6	18	5.1
Total (514 babies)	13	2.6	17	3.3	22	4.3	26	5.1

TABLE 5. Causes of death in the 26 fatalities after the first week of life in present series of 514 children of diabetic mothers.

Cause of death	Babies born before onset of mother's diabetes	Babies born after onset of mother's diabetes	Total
Malformation	2	4	6
Birth injury	1	3	4
Cyanotic attacks	—	1	1
Infections	2	8	10
Cerebellar hemangioma	1	—	1
Irrelevant disease	2	2	4
	8	18	26

One child died during an attack of cyanosis. This child was born at full term weighing 3100 g. It vomited and had diarrhea and died during an attack of cyanosis at the age of two weeks. No deformity could be seen and the parents refused to allow an autopsy.

A birth injury was the direct cause of death in 3 cases and irrelevant diseases in 4 others.

A few words will now be said about the four children who died when they were more than a year old.

The first was a boy, born in the 38th week, weighing 4500 g, to a diabetic mother. He had congenital stricture of the urethra, which

in spite of treatment led to bilateral hydronephrosis. He died at the age of 8 from uremia.

The second was a boy, normally delivered in the 39th week, weighing 4270 g, to a diabetic mother. During the first week meningococci and Erb's paralysis were observed. A neurosurgeon consulted said that there was no point in operating, and the boy died when he was 2 years old. Autopsy showed that the cerebellum and whole right cerebral hemisphere were greatly underdeveloped.

The third was a boy, born in the 42nd week, weighing 4250 g. The mother was discovered to have diabetes when he was 9 years old. Her urine contained sugar at the time of the delivery but she showed no other symptoms of diabetes. Apart from the ordinary children's diseases and an operation for hernia, the boy grew up normally. At the age of 14, he died suddenly from a hemorrhage in the cerebellum originating from a hemangioma the size of a hazel nut.

The fourth was a girl weighing 3500 g born after a normal delivery. Her mother was discovered to have diabetes 11 years later. The child died suddenly at the age of 4 from an organic heart defect.

Twenty, or a little over 75 per cent, of the 26 children who died after the neonatal period were boys. The sex distribution at birth of the whole series did not differ from normal.

Diabetes mellitus

Only one case of diabetes mellitus occurred among the 514 children, corre-

sponding to 1.9 per thousand. This was a boy born 5 years before the disease was discovered in his mother. There was no other case of diabetes either in her family or her husband's. The boy was born at full term weighing 3530 g. The delivery was normal and the child developed normally and was quite healthy until he got diabetes at the age of 12.

Another boy was given special study because it was thought that there was a large chance of his having diabetes. He was born in the 37th week weighing 4580 g. His mother had then had diabetes for 3 years and there were a great many cases of this disease in her family. The paternal grandmother of the boy also had diabetes. During an infection at the age of 3, sugar was found in the boy's urine. After thorough medical analysis, however, it was concluded that he did not have diabetes.

Heredity for diabetes

As mentioned, all the mothers had or later got diabetes. None of the fathers had diabetes. We shall now investigate the occurrence of diabetes among the other relatives of the present children.

In 100 cases we did not succeed in getting satisfactory information either about the mother's or the father's family. Information was obtained not only about the parents and grandparents but also about aunts and uncles and cousins. Diabetes starting late in life was also included. The familial occurrence in the families of the remaining 511 children is seen from Table 6.

These 511 included 162 of the 215 children born before the mother got diabetes. In 89 of these 162, or 54.9 per cent, none of the other relatives of the child were known to have had diabetes. Only in 3 cases, or 1.9 per cent, had diabetes occurred in the families of both parents. In another 56 cases, or 40.7 per cent, it had occurred in the family of one of the parents.

Information in this respect was obtained for 349 of the 396 children born after the mother got diabetes. In 173 of the cases, or 49.6 per cent, none of the other relatives of the child were known to have had diabetes. In 31 cases, or 8.9 per cent, diabetes occurred in the families of both parents. In another 139 cases, or 39.8 per cent, diabetes had occurred in the

TABLE 6. Occurrence of diabetes in family of 162 children born before and 349 born after onset of diabetes in mother.

Diabetes		Children born before onset of mother's diabetes		Children born after onset of mother's diabetes		Total	
In father's family	In mother's family	No.	%	No.	%	No.	%
+	+	3	1.9	31	8.9	34	6.7
+	-	7	4.3	15	4.3	22	4.3
-	+	49	30.2	112	32.1	161	31.5
-	-	89	54.9	173	49.6	262	51.2
?	+	10	6.2	12	3.4	22	4.3
?	-	4	2.5	6	1.7	10	2.0
Total		162	100.0	349	100.0	511	100.0

father's family or another member of the mother's family.

Other endocrine disorders

In our previous study (1957) of children of diabetic mothers, careful pediatric examination had not revealed any endocrine disorders apart from the one case of diabetes mellitus. Though we were on the lookout for disorders of this kind this time, too, we only encountered two cases.

One was a girl born at term weighing 5330 g. In spite of the child's size, the delivery was normal, except that the child got a clavicular fracture, which healed without complications. The mother had then had diabetes one year. There was no other instance of the disease in the family of either parent. Since the age of 4 months this child had been getting thyroid preparations because of athyrosis. At the time of the follow-up she was 6 years old and had developed normally with constant thyroid medication.

The other was a boy, born in the 37th week weighing 3100 g. The mother had then had diabetes for 4 years. A maternal aunt also had diabetes, but no other cases were known of in either the mother's or father's family. The boy was inclined to be fat as a child. When he was 13 years old he was admitted to the medical department of a university hospital, where it was discovered that he had not passed the five year old stage in sexual development. After treatment, he began to develop normally and at 16 he was considered to be normally developed for his age. At the age of 23 he was examined by a physician and found to be healthy and normal. He then weighed 58 kg and was 164 cm tall.

Mental defects

No serious mental defects were detected in the children. Seven cases of mental deficiency were found, but none of these

children were so retarded that they were graded as imbecile. This bears out the results in our earlier follow-up study (1957).

Deformities

One of us (Hagbard) found a deformity rate of 6.3 per cent among the children of the diabetic mothers. This figure covered the serious deformities discovered during the neonatal period. The corresponding figure for the children born before their mothers got diabetes was 4 per cent (Hagbard, 1958). Our re-examination revealed a number of deformities which were not discovered until later on.

Thus 6 deformities were found later among the 164 children born before the onset of the diabetes in the mother, corresponding to a rate of 3.7 per cent. The neonatal rate was 4 per cent. The total rate of deformity among these children amounted to 6.5 per cent. The types of deformity noted in this series are shown in Table 7.

TABLE 7. *Malformations in present 514 children who had diabetic mothers and who survived the first week of life.*

Type of malformation	Babies born before onset of mother's diabetes	Babies born after onset of mother's diabetes	Total
Organic heart defect	4	2	6
Kidney defect	1	—	1
Meckel diverticulum	1	—	1
Congenital amblyopia	—	1	1
Hydrocephalus	—	1	1
Congenital deafness	—	1	1
Urethral stricture	—	1	1

Two of the 6 children are living. One child has a defect in the interventricular septum, and one child was operated on at the age of 7 for a Meckel diverticulum but was otherwise healthy. One child died at the age of 4 months and another at the age of 4 years from a heart defect. One child died at the age of 3 weeks because of cerebral thrombosis, and autopsy revealed congenital heart defect. The last child died from a severe infection and autopsy revealed a greatly malformed left kidney.

Six deformities were also found after the neonatal period among the 350 children born after the onset of the diabetes in the mother, corresponding to a frequency of 1.7 per cent. The neonatal rate was 6.3 per cent. The total deformity rate in these children was 7.6 per cent. Table 6 shows the different deformities present.

Three of these children are living. One child was found to have congenital amblyopia. The mother had not had rubella or any other infectious disease during pregnancy, there was no toxoplasmosis and nothing abnormal was seen in roentgenograms of the skull. The ophthalmologist therefore concluded that the amblyopia was caused by faulty development of the optic nerves. Another of the living children was found at the age of one year to suffer from intense external and internal hydrocephalus. This child was an idiot and was taken care of in an institution. The third living child was completely deaf and probably suffered from aphasia as well. This child, 3 years old, had also had peripheral facial paralysis since birth. Two of the dead children with deformities died in early infancy from serious heart defects and the third died of uremia at the age of

8, caused by bilateral hydronephrosis resulting from congenital stricture of the urethra.

Other severe physical defects

In 3 cases there was a severe permanent defect which was probably caused by a birth injury. The mothers of these 3 children all had full-blown diabetes when they were pregnant and each had a difficult delivery because the child was so large. Two of the children had a useless paralyzed right arm but were otherwise healthy. The third child had epilepsy of traumatic origin.

Growth

In our previous study (1957) we measured the height and weight of the children. The values obtained for each child were compared with the average values for their age given by Broman, Dahlberg & Lichtenstein (1940), and the standard deviation of the differences was determined. We then found that the average stature of the 38 children born after the onset of the diabetes in the mothers was significantly shorter than the normal stature, but that that of the 43 children born before the onset of the diabetes did not differ from the average stature for their age. Neither group showed any definite deviations from the normal in weight.

With the present study data has been obtained about the height and weight of 201 more children born after the onset of diabetes in the mother and 25 children born before the onset of diabetes. Thus we now have data about the stature of 239 children with an average age of 5 years born after the onset of the diabetes and of 68 children with an average age of 16

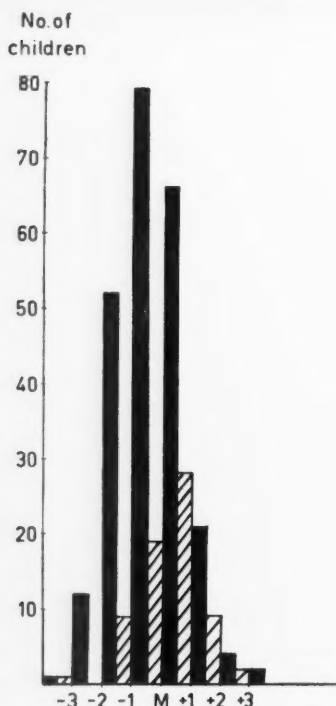


Fig. 3. Distribution of the standard deviations of the differences between the height of the 307 children at the time of the follow-up study and that of average children of their age. The obliquely lined columns representing the babies born before the onset of the mother's diabetes and the black columns the babies born after the onset of the mother's diabetes.

born before the onset of diabetes in the mother. The age distribution in these two groups is seen from Fig. 2.

This much larger series also shows deviations from the normal (Figs. 3 and 4). Thus the children born after the mother got her diabetes were both significantly shorter and heavier than normal ($P < 0.001$). The children born before the onset of the diabetes in the mother, on the other hand, showed no deviation from

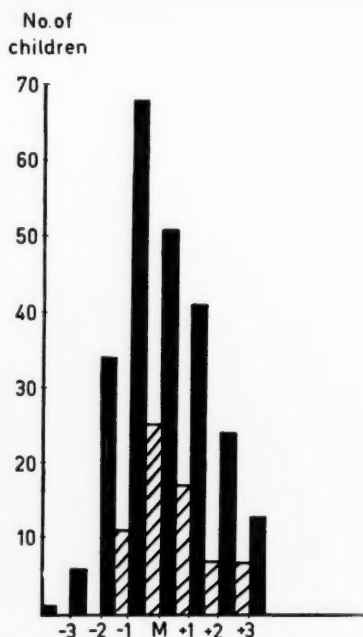


Fig. 4. Distribution of the standard deviations of the differences between the 307 examined children and a normal series in the relationship between height and weight. The obliquely lined columns representing the babies born before the onset of the mother's diabetes and the black columns the babies born after the onset of the mother's diabetes.

the normal values ($P > 0.1$). When comparing the two groups, however, the difference in their average ages must be remembered, the children born after the onset of the diabetes being naturally much younger than the ones born before. We were not able to get sufficient information about the older children's height and weight when they were younger.

Discussion

We found one case of *diabetes mellitus* in our earlier series (1957) of 123 children

of diabetic mothers. This series was carefully examined by us personally, and 87 of the children who had reached the age of 5 years were given a glucose tolerance test. Though the average age of the children only amounted to 14 years, we concluded that the diabetic rate was low amongst the children of diabetic mothers. This conclusion was born out by the present series of 514 children. It is true that these children had a low average age, (8 years). Nevertheless, 139 of them, or a little more than a fourth, had reached the age of 11 at the time of our study and half of these were more than 15 years of age (Fig. 1). As yet, only one of these 514 children has got diabetes; this was discovered when he was 12 years old. This corresponds to a rate of 1.9 per thousand. The diabetic rate in a normal Swedish population has been given as 4.9 per thousand (Dahlberg, Jorpes, Kallner & Lichtenstein, 1947).

Naturally it is impossible to compare these rates directly because our series has a lower average age than that of a normal population. The rate in a Swedish normal population between the ages of 5 and 10 years has been given as 1.1 per thousand (Dahlberg, Jorpes, Kallner & Lichtenstein, 1947). As the average age of our children was 8 years and the diabetic rate there 1.9 per thousand, the rate could not be said to be abnormally high in our series. Naturally it cannot be said how much the rate would increase with the passage of time, for according to Joslin (1952) about three-quarters of all cases of diabetes start after the age of 35. On the other hand, there is no reason to assume that the diabetic rate for different ages is different in children of diabetic mothers than in other

children (Grunnet 1957). It is true that Hoet (1954) believed that the Langerhans' islands in the fetuses of diabetic mothers are often injured because the mothers get too little insulin while they are pregnant, and that this together with hereditary factors causes diabetes to appear earlier in these children. But this was not borne out by our series.

The *hereditary conditions* in diabetes mellitus are not yet clear. The etiology and pathogenesis probably vary in different cases, making the results of hereditary studies difficult to interpret or misleading. The size and the composition of the material studied has a great influence on the results, as Grunnet (1957) has recently shown. He concluded in his monograph on the heredity in diabetes mellitus that most cases of this disease, at any rate most of the severe cases, are ones of primary pancreaticogenic diabetes, probably inherited recessively, and that some of the mild cases in elderly persons are probably of exogenic nature.

Data was obtained concerning the occurrence of diabetes in the mother's and father's family in 511 of our cases. All the mothers of these children were diabetic or became so later. None of the fathers had diabetes at the time of our study. In 183 of the 511 cases, or 35.8 per cent, diabetes occurred only on the mother's side. Diabetes occurred on the father's side in 22 cases, or 4.3 per cent and in 34 cases, or 6.7 per cent, on both sides. Thus 46.8 per cent of the children had other relatives with diabetes on one or both of their parent's sides.

It seems to us that there were an unusual number of diabetes among the other relatives of these children. Unfortunately,

we could not find any other figures with which we could compare ours, as all the other series were composed in a different manner. However, we did not find an unusually high diabetes rate among the children themselves. Even though the rate might rise to abnormal proportions as the years pass, the chances of the children getting diabetes seem to be so small that one cannot advise a diabetic woman against having children for this reason. It is another thing if the husband also has diabetes or if there are a great many cases of the disease on both sides or if the diabetes on one or the other side occurs in every generation or the husband and wife have already had one or more diabetic children (von Hofsten, 1948; White, 1952; Grunnet, 1957). Otherwise we agree with v. Verschuer (1941-1942) and Grunnet (1957) that the great possibility of begetting healthy children should be emphasized, and with Grunnet that the risk of passing on the disease seldom justifies sterilization.

Besides the child who had diabetes, only two cases of *endocrine disorder* were encountered, one girl who had athyreosis and one boy who was retarded sexually but became normal with treatment. Thus our series did not show a definitely unusual amount of other endocrine disorders. Unfortunately, we did not have enough data to be able to study different endocrine functions, e.g. the age at the onset of puberty.

Our series did not indicate that severe *mental defects* occur more often among the children of diabetic mothers than others.

It has already been shown that the children of diabetic mothers are more often deformed than others. Thus one of us

found a *deformity rate* of over 6 per cent in children born before the onset of diabetes in the mothers (Hagbard, 1956) and of 4 per cent in children born after the onset of the diabetes (Hagbard, 1958). These rates refer to deformities discovered during the first seven days after birth. The rate rose slightly as the children grew older. Thus the total deformity rate amounted to about 7 per cent and seemed to be about the same whether the child was born before or after the onset of the diabetes in the mother. Most of the deformities were so serious that they were soon noticed and soon led to death. There is therefore no reason to expect that the deformity rate would rise much with the passage of the years. All except 2 of the 12 deformities discovered after the neonatal period were discovered during the first year. It is worthy of note that half of them were heart defects, which are often not discovered during the neonatal period. The children surviving the first year probably have no more deformities than other children.

Hoet (1957) stated that the congenital deformity in the children of diabetic and prediabetic mothers was often caused by insulin deficiency and that it was therefore important to give the mother sufficient insulin, especially during the first few months of pregnancy. If this hypothesis were true, the deformity rate should be greater among the children whose mothers had fullblown diabetes than among the children whose mothers did not get diabetes until after they were born. This was not the case in our series, however, the rate being about the same in both groups. An increased deformity rate has even been observed among children born

more than 5 years before their mothers got diabetes (Hagbard, 1958). Still, this does not belie the hypothesis that the deformities are caused by an insulin deficiency. Some so-called prediabetic mothers probably suffer from temporary diabetes during their pregnancy but the disease is not detected and so not treated. Again, some women with fully developed diabetes are probably careless or neglectful about their treatment. Thus, it may be that there are just as many cases among the prediabetic as diabetic pregnancies in which the mother does not get a sufficient amount of insulin while she is pregnant. However, as the mother's need of insulin seldom increases, but more often remains unchanged or decreases during the first months of pregnancy, when according to Hoet the fetus is most susceptible to lack of insulin, we are not yet convinced that Hoet's theory is correct.

As regards the connection between maternal diabetes and *the growth of the child*, two facts are known: firstly that mothers who have or later get diabetes tend to give birth to large babies and, secondly, that children with juvenile diabetes are often retarded in development (Bergqvist, 1954). It is surprising, however, that our healthy children of diabetic mothers had a lower average height and higher weight than normal in the age groups we studied (average age 5 years). On the other hand, the children of the so-called prediabetic mothers did not differ from other children in these respects. It must be remembered, however, that these children were 16 years old, on the average.

Most of the children who died after the first seven days died before they were one year old. Thus, while the *mortality*

amounted to 5.1 per cent for all the children, 4.3 per cent was caused by children regarded less than one year old and only 0.8 per cent by the children who lived longer. Half of the 26 deaths occurred during the first month of life.

As one of us (Hagbard, 1956) has shown, the neonatal mortality among the live-born children of these diabetic mothers amounted to about 14 per cent. Thus the total infant mortality during the first year amounted to about 19 per cent. This rate greatly exceeds the 2.5 to 3.5 per cent infant mortality found in normal Swedish series (Åkerrén, 1956). However, the infant mortality during the first year in the children of diabetic mothers has decreased during recent years. Stendahl (1952) found a death rate of 29 per cent during the first year among 116 liveborn children, 18 per cent shortly after birth and 11 per cent later. It must be remembered, however; that both Stendahl's and our series were collected over a long period of time and that the infant mortality has dropped considerably all over the country during the last decades, no doubt also to the advantage of the children of diabetic mothers. However, these children probably still die much more often in infancy than other children. We shall now discuss a few of the reasons for this.

A large number of the deaths are caused by deformity, unfortunately of a kind seldom amenable to therapy. The deaths caused by birth injury can probably be cut down by giving more thought to the best time and best mode of delivery for the individual case, consideration being given to the size and maturity of the fetus and other factors. In all 4 cases in our series in which the child died from a

birth injury, and in the 3 cases in which the child was severely handicapped by a birth injury, the large size of the child had made the delivery very difficult.

Ten of the 26 deaths were caused by infection. Severe infections were most apt to occur in the premature children and immaturity in the child often contributed toward its death. It is important, therefore, not to induce the delivery too early in diabetic mothers, preferably not before the 37th week for, as one of us (Hagbard, 1956) has demonstrated, before this time there is a large risk of the child dying early in life.

The investigation has shown that the prognosis is good for the children of diabetic mothers living beyond the first seven days. The death rate is higher than normal

during the first year but, next to deformity, most of the increase is probably due to birth injuries and prematurity. If more consideration is given in the individual case to the best time and mode of delivery, judging by the size and maturity of the child and other factors, it should be possible to cut down both the neonatal deaths and the deaths later on in the infant year. In our series, 95 per cent of all the children surviving the neonatal period are alive and 92 per cent of the children were quite healthy. It may be that these children will show a higher than normal diabetic rate later on in life but apart from this it is our opinion that the prognosis for children of diabetic mothers who live to be more than one year old is not different from that of other children.

Summary

A follow-up study was made of 514 children of diabetic mothers surviving beyond the first seven days of life, of which 164 were born before and 350 after the onset of the diabetes in the mother. The average age of these two groups was 15 and 5 years, respectively. The study showed that the prognosis for these children was good. Apart from an increased death rate during the first year of life the prognosis for children of diabetic mothers probably does not differ from that of other children, though it may be that they are more inclined to get diabetes later on in life.

Etude sur 514 enfants de mères diabétiques.

On a suivi 514 enfants de mères diabétiques ayant survécu les premiers sept jours après la naissance, dont 164 sont nés avant et 350 après le développement du diabète chez la mère. L'âge moyen de ces deux groupes était respectivement 15 et 5 ans. L'étude a démontré que le pronostic, concernant ces enfants, est bon. A part une augmentation du taux de mortalité pendant la première année de vie, le pronostic ne diffère pas de celui d'autres enfants, bien qu'ils soient probablement plus susceptibles de devenir diabétiques plus tard dans la vie.

Nachuntersuchungen von 514 Kindern diabetischer Mütter.

Eine Nachuntersuchung wurde an 514 Kindern diabetischer Mütter durchgeführt, welche die ersten 7 Lebenstage überlebten, unter denen 164 vor und 350 nach dem Beginn des Diabetes bei der Mutter zur Welt gekommen waren. Das durchschnittliche Alter bei diesen zwei Gruppen war 15 beziehungsweise 5 Jahre. Das Studium zeigte, dass die Prognose für diese Kinder gut sei. Abgesehen von einer grösseren Sterblichkeit während des ersten Lebensjahres unterscheidet sich die Prognose für Kinder diabetischer Mütter wahrscheinlich nicht von der anderer Kinder, obwohl die Möglichkeit besteht, dass sie eine grössere Neigung zur Zuckerkrankheit im späteren Leben haben.

Estudio continuado de 514 niños de madres diabéticas.

Se realizó un estudio continuado de 514 niños de madres diabéticas que sobrevivieron a la primera semana de vida, de los cuales 164 nacieron antes del comienzo de la diabetes materna, y 350 después. La edad media de estos dos grupos era de 15 y 5 años respectivamente. Este estudio demostró que el pronóstico para estos niños era bueno. A excepción de un aumento de la mortalidad durante el primer año, el pronóstico de los niños de madres diabéticas no difiere probablemente del de otros niños, aunque puede ser que tengan mayor tendencia a la diabetes ulteriormente.

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Pediatric Clinic
Barnsjukhuset
Göteborg,
Sweden

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Meeting October 23, 1958

G. Sterky: Diagnostic and therapeutic aspects of reticuloendotheliosis

A brief survey is presented of the classification of diseases in lymph glands and the reticuloendothelial system. The question of nomenclature is discussed and the term "nonlipid histiocytosis" is defined to include eosinophilic granuloma, Hand-Schüller-Christian's disease and Letterer-Siwe's disease. Six cases are reported with special emphasis on the early symptom of therapy-resistant eczema in the scalp and the auditory meatus. Monocytosis in the peripheral circulation and electrophoresis findings, especially related to the gamma-globulin fraction, are discussed. The value of skin smear as a diagnostic aid is elucidated and the possibility of employing it as a "screening test" in intractable seborrheic eczema is discussed. A description is given of the effect of treatment with steroids and roentgen. Scintigram following the intravenous injection of radio-active colloidal gold was determined in 2 cases for the purpose of examining the possibility of employing this material in the treatment. The prognosis of "nonlipid histiocytosis" is not wholly grave, for which reason all therapeutic resources should be utilized.

DISCUSSION.—**B. VAHLQUIST:** Strong monocytic reactions may be observed in other conditions as, for example, "compensatorily" in grave granulocytopenias.

U. Müller-Eberhard: Importance and detection of abnormal hemoglobins

A brief survey is given of the most frequent hemoglobin disorders encountered in various parts of the world. Attention is called to the difference in clinical manifestation of a homozygous and a heterozygous carrier of an abnormal hemoglobin gene. While homozygotes may suffer from a severe hemolytic anemia, heterozygotes are mostly completely asymptomatic. Also an individual having two different abnormal hemoglobins may have rather severe clinical symptoms. Since we can only offer palliative treatment, it seems of importance to diagnose the heterozygous carrier of an abnormal hemoglobin gene in order to inform and to advise heterozygotes when they want to marry and to have children. Methods suitable for the detection of abnormal hemoglobins are discussed. The fact should be emphasized that electrophoresis using paper as a supporting medium may fail to detect an abnormal hemoglobin. On the other hand, starch-block electrophoresis allows detection and differentiation of most of the normal and abnormal hemoglobin components. Hematological findings suggesting the presence of an abnormal hemoglobin are: (1) Chronic therapy-resistant anemia when serum iron and total iron-binding capacity are normal; (2) changes of red-cell morphology such as aniso- and poikilocytosis, microcytosis and target cells; (3) increased resistance of the

red cells to hypotonic saline solutions. If several of these symptoms are found, especially if they are also found in other family members, an investigation for an abnormal hemoglobin should be initiated.

That hemoglobin disorders do occur in the Scandinavian population is demonstrated by the observation of two Swedish carriers of the abnormal hemoglobin H. Both patients belong to the same family (cf. *Acta paediat.*, Nov. 1958).

P. O. Hillborg: Skeletal changes in Gaucher's disease

An accumulation occurs in Gaucher's disease of cerebroside in the reticuloendothelial cells in the spleen, liver and bone-marrow. As the cerebroside accumulation in the bone-marrow advances, skeletal changes occur: thickened lower metaphyses of the femur, bone necroses in the head of the femur, vertebral destructions and osteoporotic rarefactions in the long bones of the extremities. Some investigators maintain that the skeletal changes would be accelerated by splenectomy. The author's material comprises 20 cases. Seven of these, in whom splenectomy was not attempted, died before 3 years of age. Four operative cases also succumbed before this age. None of the deceased presented any bone deformities. Among the 8 operated and surviving cases, 7 had enlarged spleens since 1 year of age. Splenectomy was performed at different ages, 1-15 years after the onset of the disease. The initial bone deformities were observed 1-3 years after the operation and appear to have been more dependent on the time of the latter than on the onset of the disease. This may suggest that they were accelerated by the operative intervention. Six cases were examined for the appearance of cerebroside in the blood. Each one showed an increment of this material in the plasma. These studies indicate that in Gaucher's disease we are dealing with a disturbance in the intermediary lipoidal metabolism, with an extravasation of cerebroside in the plasma, a phagocytosis of the material in the reticuloendothelial

cells, mostly in the spleen, but also in the bone-marrow and liver. When the spleen is extirpated, it would appear that the accumulation in the bone-marrow is accelerated, and thus the bone deformities proceed at an increased rate. Of course, one should not on this account desist from performing splenectomy in those cases where a marked splenomegaly has produced a life-threatening pancytopenia.

F. Geubelle and G. Wallgren: Some aspects of the respiratory mechanism in congenital heart-failures

The purpose of the investigation has been to study eventual changes in the lung's mechanical properties induced by the state of disturbed circulation in congenital heart-failures. The lung's compliance was measured in connection with the catheterization of the heart by means of simultaneous registration of the respiratory volume and the intra-esophageal pressure variations. A total of some thirty children aged 1 month to 14 years were examined, and they represented different forms of altered pulmonary hemodynamics. These investigations showed without exception that a tendency to a lowered lung compliance is present in children suffering from heart failure, i.e., greater effort is required for the necessary expansion of the lungs to bring about adequate ventilation. The connection between this increased lung inflexibility and state of pulmonary circulation is discussed.

B. Lindquist: Studies of digestion in children with steatorrhea

Studies are made of the composition of the intestinal content from different levels of the intestinal tract during *progressive* digestion and resorption. The child is given a test meal of known composition. As the food passes down through the intestine, a certain part of the food mixed with intestinal juices can be made to run backwards through a tube. The sample of intestinal content is

examined for the presence of fat, carbohydrate, radio-activity from I^{131} -tagged protein, trypsin, amylase, bile-pigment material (determination of optic density at 400 $m\mu$) and polyethyleneglycol (PEG, a non-resorbing substance in the test meal). The presence of PEG in the test meal makes it possible to determine the percentage resorption of the different foodstuff ingredients at different intestinal levels. These studies were carried out partly on normal children and partly

on children with different forms of steatorrhea—cystic fibrosis of the pancreas, celiac disease and conditions with obstructed flow of bile into the intestine—and the results obtained are discussed against the background of the pathophysiological disturbances in these diseases. The total impression gathered about the functional capacity of the digestive canal serves as a clear indication in the differential diagnosis between different forms of steatorrhea.

Meeting October 24, 1958

N. O. Ericsson, G. Laurell and J. Winberg:
Aspects of treatment of urinary infections in children

(To be published under Progress in Pediatrics in *Acta pædiatrica*, 48, 1959.)

Birger Broman: Prognosis for the fetus by immunization of the mother

It has been known for some time that the serious, familiarly occurring, so-called erythroblastosis disease in the newborn is most often due to Rh-immunization. Still, in these cases it is not only the difference in the Rh-groups (mother Rh-negative, child and father Rh-positive) which influences the origin and effect of Rh-immunization: extensive materials have shown that other blood-group genes too may greatly affect the pathological process in iso-immunization. A more complete analysis of blood-group genetics than a sole determination of Rh(+) and Rh(-) may thus supply a further lead in ascertaining the risk an expected child runs of contracting a grave erythroblastosis disease. These conditions hold not only theoretical interest, but should be borne in mind when the decision is made about indications for the possible termination of pregnancy when it is a case of Rh-immunization. Some experiences with iso-immunization within other blood-group systems than Rh were discussed.

B. Hagberg, P. Sourander, L. Svennerholm and H. Voss: Late infantile metachromatic leucodystrophy of genetic type

Clinical, histological and neurochemical investigations were made on three boys, two of them brothers, the third one second cousin to the others. The disease started with gait disturbances at about 1½ years of age and there were progressing neurological signs until death at 3½, 4 and 5½ years respectively. In the white matter the myelin sheaths and partly the axons were destroyed and replaced by large amounts of PAS-positive granular bodies. The same bodies occurred also in the cortex and basal ganglia, liver and kidney. No oligodendroglia cells were found in the affected white matter. Clinically and histologically the cases in many aspects corresponded to those described by Greenfield (*Brain* 73, 291 (1950)). Chemically the total lipids, mainly the glycerophospholipids, were reduced in the grey and white matter. The total amount of sphingolipids was within normal limits, but there was a tremendous increase of sulfatides.

(To be published in *Acta pædiatrica*.)

I. Alm: Experiments with a *Lactobacillus bifidus* factor

During recent years and after much preliminary work, a series of *L. bifidus* stimulating factors have been isolated by investigators on both sides of the Atlantic. We are

mostly concerned with substances which *in vitro* promote the growth of certain types of *L. bifidus* that, however, are not present in the stools of infants. A number of strains have been successfully cultivated in recent years, which have different requirements for their appearance, but otherwise dissimilar properties. Petuely in Graz, who has worked on the problem for more than a decade, has succeeded in developing a substance closely related to lactose, called lactulos, which acts stimulatingly on the intestinal *L. bifidus* flora, after which a *L. bifidus* type having properties similar to the usual type present in breastfed infants appears, provided that the lactose/albumin quotient in the food is greater than 2.6. This factor has just been produced and I have obtained certain quantities for tests on a modest scale. In view of the promising results, I am submitting a preliminary report of experiences with an infant food containing this factor.

DISCUSSION.—*B. Vahlquist*: During the last few years the question about the *L. bifidus*-stimulating factors has attracted considerable attention. The one isolated by György stimulates also a special type of *L. bifidus*. The whole problem is perhaps now in rapid process of disentanglement.

H. Enell, K. Kaijser and L. Söderhjelm: Occurrence of gonadal dysgenesis in Sweden

The disease syndrome, which during recent years has most often been described under the term gonadal dysgenesis, had earlier been published under such names as dystrophia brevicollis, sexual infantilism, agenesis ovarii and Turner's syndrome. Some few years ago it was considered possible by means of a certain technique to determine a person's genetic sex by observing the changes disclosed by studying chromosomes in the cells. The interesting thing with reference to Turner's syndrome is that in the majority of these apparently sexually underdeveloped girls, determination of the genetic sex has disclosed that it is really a question of gonadal dysgenic boys and that these in-

dividuals thus have a genetic male sex. The morbid-state designation gonadal dysgensia would therefore appear to be the most correct term. It seemed appropriate for us to attempt to ascertain how many cases of gonadal dysgenesis could possibly be known nowadays in Sweden. An inquiry among all physicians-in-chief on the children's and gynecology departments in the hospitals in Sweden revealed that at present some 40 cases of this syndrome are probably known. Laparotomy or autopsy was performed in 12 cases and thus the diagnosis was established with certainty. The genetic sex was determined in 10 cases and 7 of these proved to be males. The syndrome occurs throughout Sweden, but with regard to the population density in different parts of the country there is obviously a certain increase of the frequency of the syndrome in the northern part of Sweden. Thus 17 of the 40 cases are found in the 3 northern provinces. In order to get an idea of how many patients might possibly turn up every year with this syndrome, an investigation was made of the year of birth of the 40 known cases. This revealed that an obvious increase of the appearance of this syndrome occurred during the 1935-1945 period.

DISCUSSION. *B. Vahlquist*: Does any racially conditioned variation exist in the frequency of the disease? — *K. KAISER*: There seems to be no possibility, on the basis of our material, of evaluating the occurrence of gonadal dysgenesis from a racial point of view. The genetic, cellular sex-determinations in our cases were made either by Dr. Paul Riis in Gentofte, Denmark, or in the Institute of Racial Biology by Professor Böök in Uppsala. The occurrence of more or less definite heart-diseases in our series was estimated to approximately 5 out of 40 cases. At least 3 were definite cases of coarctatio aortae. A closer analysis of possible kidney malformations (by means of urogram or similar tests) was apparently not indicated in our cases. Thus no information can be obtained on kidney anomalies, but it would seem advisable to make urograms routinely in these cases.

M. Michaëlsson: EKG-studies during the first week of life

Fifty-six healthy children of healthy mothers with uncomplicated delivery were examined. Twelve leads were registered, namely I, II, III, avR, avL, avF, V_1 - V_6 . ECG were taken immediately after delivery and in all cases generally on 5 occasions during the first week of life. During the same registration occasion the heart-frequency usually varied very markedly, and differences of 70-80 beats/minute were not uncommon. The minimum frequency was 65 and the maximum 200. More pronounced sinus arrhythmia was observed in 16 cases. In addition other rhythm disturbances occurred in 18 cases. Most of these were of the supraventricular arrhythmic type in whom the variations in rhythm seemed to run parallel with changes in the degree of wakefulness. These rhythm changes were usually observed on the second and third day of life and had disappeared in all but two cases on the seventh day of life. One case with numerous ventricular extrasystoles was observed. The ECG became normal in this case on the fourteenth day of life. Concerning the duration and amplitude of P, P-Q-time, duration and amplitude of QRS, no apparent difference was observed in comparison between different days of life. The T-wave was low in the standard and unipolar extremity leads in all cases during the first day and increased successively in amplitude.

DISCUSSION.—*John Lind:* Information accumulated would indicate that the cardiovascular system of the normal newborn infant adjusts gradually over a period of several days rather than within minutes after birth as was previously supposed. The switch-over from the fetal type of circulation to the newborn is probably brought about by the following factors: an increase in systemic resistance, a decrease in pulmonary resistance, an increase in the arterial oxygen saturation, and other less well-defined factors. Associated with these fundamental changes in the cardiovascular system is the presence of a large left-to-right shunt through

the ductus arteriosus at rest, and a right-to-left shunt with crying, and a ventricular and pulmonary artery hypertension. The methods used to determine the neonatal circulatory changes are complex and expensive, and others should be developed. For these reasons it is of interest to evaluate the role of the electrocardiogram in such studies. We have studied the electrocardiographic changes in the normal infant during the first ten days of life. Thirty infants were studied longitudinally, and seventy two were studied cross-sectionally. The physiological response of the latter group of infants to administration of 10% and 100% oxygen by mask and to adrenaline acetylcholine was measured recording unipolar lead V_1 . We have been specially interested in the significance of the changes of the T-wave during the neonatal period. Specifically in regard to the T-wave in unipolar lead V_1 it was regularly positive under 12 hours of age and negative or diphasic after 5 days of age. It is interesting that these two phases were gradual and took place over the same time interval in which the pulmonary hypertension normally disappears. Evidence of right ventricular hypertrophy, however, persisted throughout this entire period without significant changes. Administration of adrenaline to infants with presumably normal pulmonary artery pressures frequently produced changes in T-wave of the electrocardiogram similar to those found in infants with pulmonary hypertension. — *Å. Lundberg:* Especially during the newborn period, when the pathological high frequencies in tachycardias make it more difficult or impossible to form an opinion about the auricular complex in the ECG, registration with the esophagus electrode is valuable. The P-notch appears here more distinctly, which may be demonstrated in comparison with simultaneously registered standard and precordial leads.

R. Berfenstam and P. Å. Wikander: A Swedish poison information centre

The authors have cherished for some years the idea of founding in Sweden an information centre dealing with poisons. De-

tails were discussed at a meeting with the Section of Pediatrics in February 1958. The work of systematically collecting and preparing information about the composition of chemotechnical products—cleaning-materials, cosmetic articles etc.—commenced in the Children's Clinic at Karolinska sjukhuset and has been intensified during recent months, thanks to the economic support granted by the Swedish Red Cross. Available

facts are being noted on indexed cards. Information about poisonous plants are likewise being registered. Even about plant-protective products useful information is being gathered. The authors anticipate shortly to be able to provide the medical profession with useful information whenever poisoning has occurred with such products and when doubt is felt about the product's actual poisonous nature.

Meeting Nov. 14, 1958

G. M. Ardran, F. H. Kemp and J. Lind:
A cineradiographic study of bottle feeding and breast feeding

It is widely believed that a baby obtains milk from a bottle by sucking the contents through the teat, and that in doing so it contracts the muscles of the cheek, lips and tongue, so as to produce a partial vacuum. Cineradiographic study of infants taking food from a bottle has indicated that these views are not entirely correct. The observations made indicate that at suckling the neck of the teat is occluded by approximation of the jaws and the contents of the bulb are expressed into the mouth by elevation of the tongue towards the soft palate, the tongue indenting the bulb from its neck backwards. During the phase of compression of the bulb of the teat by elevation of the tongue in the forepart of the mouth, there is also taking place simultaneously a lowering of the tongue behind the teat which must cause some suction. When milk is swallowed, naso-pharyngeal closure is made by elevation of the soft palate against the adenoidal pad on the roof of the epipharynx. The bolus passes through the pharynx on both sides of the superior laryngeal aperture. The larynx is closed as each bolus is expressed from the pharynx and reopened just before the next bolus enters. During cineradiographic studies of breast feeding with the mother's nipple and areola coated with a paste of barium sulphate in lanoline, the following observations were made. The

nipple is sucked to the back of the baby's mouth and a teat is formed from the mother's breast. When the jaw is raised, this teat is compressed between the upper gum and the tip of the tongue resting on the lower gum. The tongue is applied to the lower surface of the teat in the backward direction, pressing it against the hard palate: the teat is reduced to approximately half its former width. As the tongue moves towards the posterior edge of the hard palate, the teat shortens and becomes thicker. When the jaw is lowered, the teat is again sucked to the back of the mouth and restored to its previous size. Each cycle of jaw and tongue movement takes place in approximately 1-5 seconds. The pharyngeal cavity becomes airless and the larynx closed every time the upward movement of the tongue against the teat and hard plate is completed. These movements are analogous to those seen in bottle feeding: they suggest that the contents of the ducts or cisterns of the teat are expressed into the mouth. The influence of suction upon the flow of milk from the teat has not been established. It is considered that suction may be exerted during the phase of compression of the teat as the tongue is simultaneously lowered behind the teat. It is suggested that the teat is formed from the nipple and the adjacent areola and underlying tissues.

DISCUSSION.—N. Malmberg: In regards to the speaker's emphasis on the tongue's work and movements against the gum for

sucking, one may ask about the role played by the movements of the lower jaw in this respect, and, to judge from the filmpictures, it must be considerable. — A. WALLGREN: This study of the sucking mechanism should among other things result in certain recommendations concerning the teat's shape. It should be soft and rather longish. Has anyone studied the sucking movements in the presence of mechanical barriers such as harelip or cleft palate?

E. B. Nordlund: The physician's view of fostering problems in connection with divorce cases

(To be published elsewhere.)

O. Broberger, F. Gyulai and J. Hirschfeld: Splenectomy and infection sensitivity

O. Broberger and F. Gyulai: Clinical study

In a critical analysis of the past eight years' published splenectomy surveys among children, comprising 470 splenectomized children, one finds serious infections during the post-operative period in 4.5% of the cases when the operation was performed after 1 year of age, and in 22.5% splenectomized during the first year of life. About one-third of the total infections after splenectomy (often meningitis, septicemia, pneumonia, some cases with fatal issue) appeared in this latter groups. Among 36 children between 1 and 14 years of age splenectomized in Uppsala and Stockholm during the past 8 years on account of microspherocytosis, thrombocytopenia or rupture of the spleen, 2 patients, during a follow-up study 3 months to 7 years after the operation was performed, showed repeated and rather severe infections (meningitis, pneumonia, upper respiratory tract infections) throughout the 5 and 9 months' observation periods respectively following splenectomy. Both were 3 years of age at the time of operation. Electrophoretic studies showed no pathological changes in 20 cases thus examined. Immuno-electrophoretic studies were made in some cases (see below). An attempt to disclose bactericidal

activity in the sera from 32 cases failed to reveal any significant changes in this activity as compared with normal control sera. On the basis of data from literature and our own observations we conclude that the risk of increased infection sensitivity may be considered slight for children splenectomized over 1 year of age on the 3 above-mentioned indications. In dealing with infants one must, according to information available in literature, reckon with the possibility of an increased infection sensitivity after splenectomy. This applies possibly also to older children with serious organic disease when this is not noticeably influenced for the better by the splenectomy.

J. Hirschfeld: Immuno-electrophoretic analysis of 16 splenectomy sera

Immuno-electrophoretic analysis of 16 splenectomy sera against an antihuman serum produced in the rabbit gave at least 19 precipitating components, which may be defined through their electrophoretic position and certain other precipitate characteristics. They may be divided into albumin, 5 α_1 -globulins, 8 α_2 -globulins, 2 β_1 -globulins, 2 β_2 -globulins, and gamma-globulin. Some of these components do not occur in all sera. Transferrin is identified through comparison with a pure transferrin preparation (Kabi). Its immuno-precipitate is distinguished in normal sera by a marked veil formation, which is an expression of an antigen-excess phenomenon. In 7 of 16 splenectomy sera this veil formation was assessed as slightly reduced, which may indicate a transferrin depression in these sera. One serum showed a markedly reduced veil formation in triplicate tests. The clinical data show that this patient has a pronounced infection sensitivity. Through the presence or absence of certain precipitates within the α_2 -globulin region, the material could be divided into 3 groups. Similar variations have later been detected even in normal sera. Subsequent studies with a commercial anti-human serum for immuno-electrophoresis, prepared by the Behring-

Werke, have further disclosed a precipitating β_2 -globulin (β_2A). This precipitate has normal appearance in 2 out of 16 sera, but is lacking in 6 and is suggested in 8 sera. Data from the literature show that splenectomy sera may lack this component and that it fails to appear in agammaglobulinemia in children under 1 year of age, and in certain syndromes with increased infection sensitivity.

DISCUSSION.—*V. Vahlquist:* This is a valuable study. It is evident that the indications for splenectomy must be severe during the first year of life. — *G. Sterky:* In the Surgical Clinic at the Kronprinsessan Lovisa's Barnsjukhus, 35 children were splenectomized during 1943–1958 due to traumatic rupture of the spleen. Several others have undergone the same operation, but on account of concurrently sustained severe traumatic injuries they succumbed within a few days. Only 8 persons have been splenectomized on "medical" indications. Three of these were under 6 months of age when operated upon. To judge from case records, it is apparent that none of the splenectomized children have sustained any serious infectious complications during the first postoperative weeks.

D. Ikkos and P. Karlberg: Exercise tolerance test and its clinical application

The patho-physiological background for an exercise tolerance test was presented briefly. The bicycle ergometer test ad modum Karolinska Sjukhuset was described. A motion picture of a test performed with a ten-year-old boy was shown. Calculated working capacity in normal children, aged 6–14 years was shown in relationship to age, weight and height. The clinical application was discussed, illustrated by studies done in children with arrhythmias and congenital heart diseases. (To be published elsewhere.)

DISCUSSION.—*H. Berven:* At the Stockholm Epidemisjukhus the method mentioned is utilized for determining the physical capacity in myocarditis in connection with acute infections. The methods have further been employed by Bengtson and Berven in

studies of the physical capacity for work in normal schoolchildren.

G. Berglund and O. Broberger: Follow-up investigation of patients with idiopathic thrombocytopenic purpura

During the years 1951 to 1958, 28 children have been treated for idiopathic thrombocytopenic purpura at the Children's Clinic, Karolinska Sjukhuset. Of these 19 were girls and 9 boys. The age at onset varied between 1 and 13 years. Nine of the cases were so mild they did not require therapy although 2 of these cases were long-lasting (1.5 and 7 years). All the other cases have had severe hemorrhages. Eighteen of them were treated with steroids, generally dexamethasone, which was given in a dose of 1 mg/kg body weight per day for at least 3 weeks. In 6 cases permanent remission occurred; the time of observation after the withdrawal of the steroids varied between 4 months and 6 years. The rest of the steroid-treated patients had only a short, temporary remission and 3 later obtained partial remission. Eight of the cases where no therapeutic effect was obtained with steroids have later been splenectomized. Five of these immediately responded with an increase in platelets and a normalized bleeding time. They have since had normal hematological values during the observation times ranging from 8 to 30 months. Of the other splenectomized patients one had a partial remission after the operation, hemorrhages ceased and the bleeding time was normalized; one had a spontaneous remission several months later; and one improved after renewed treatment with steroids. One patient, not preoperatively treated with steroids, was splenectomized with good result. Platelet agglutination was performed in 22 cases during the acute illness, and in 9 cases was positive. In the mild cases, which did not require any treatment, agglutination was always negative. In the severe cases it was positive in about half of the cases. A positive platelet agglutination should thus give support to the suspicion that one is dealing with a more severe form of idiopathic thrombocytopenia

purpura, but no indication of the long-term prognosis can be ascertained. In this group of children no complications occurred. There has been no mortality and no evidence of intracranial bleeding, which is said to be the most common cause of death in adults with this condition.

DISCUSSION.—*B. Vahlquist:* Our experiences in Uppsala coincide in most essentials with those reported by the speaker. The

steroids have not measured up to our anticipation. We seldom perform splenectomy any more before the disease has lasted 6 months. — *G. Sterky:* How many of the speaker's cases occurred after a virus infection and how much time elapsed between the initial symptoms and the operation? Wintrobe among others has stressed the good prognosis in cases occurring in connection with a virus infection.

M. d'Avignon, Stockholm

Pediatric Society of South Sweden

Meeting June 8, 1958

John Ingvar Ek: The etiology of mongolism

Three principal lines have long been distinguishable with regard to the etiology of mongolism: (1) the genetic, (2) infections in the mother during pregnancy, (3) endocrine disturbances in the mother during pregnancy. More recently it has been found that thyroid hyperfunction is typical in mothers of mongoloid children. Thus these women have an abnormally high frequency of goiter and morbidity of hyperthyroidism and a pathologically high mean value of the protein-bound iodine in the serum. It is hardly likely that the thyroid hormone is the injurious agent. Firstly this protein molecule is entirely too large to pass the placenta; secondly it has been shown that the fetal and maternal blood iodine levels are largely independent of each other. A more plausible assumption is that these women in addition to their thyroid hyperfunction have a disturbed corticoid pattern. The corticoid level rises, of course, during pregnancy, and these hormones may readily be conceived as passing over into the circulation of the fetus. They constitute, in the pattern of fetal development, high-potential substances through their effect on mesenchymal proliferation. The numerous observations that mothers have had mongoloid children after infections or exposure to other stress factors in the beginning of pregnancy are also explainable by the assumption of the patho-

genic significance of the corticoids. Hereditary data in connection with mongolism, such as the somewhat increased risk for siblings of mongoloid children, do not conflict with the assumption that humoral factors are the active causes of the abnormal development of the fetus. It is known from animal experiments producing cleft palate that the sensibility to the teratogenic effect of cortisone varies greatly in the different, genetically pure mouse strains. The genetically determined constitution must be thought of as responding in an individually varying manner to different external influences. An optimal combination between the genotype of the fetus, the endocrine disposition of the mother and the exogenous releasing factor could be the prerequisite for the occurrence of mongolism. In this manner are explained, firstly, the slight hereditary disposition found in mongolism and, secondly, the freakish, sporadic occurrence of the disease. In order to determine whether deviations in the corticoid pattern actually exist in women who have given birth to mongoloid children, an investigation of the corticoid pattern in the urine of such women has been carried out. Some 20 mothers were subjected to two examinations each. With regard to the 17-ketosteroids and 17-ketogenic steroids there were no abnormal findings, whereas two special corticoid fractions showed pathologically increased values.

Meeting October 5, 1958

S. Hermansson: Two cases of adrenal apoplexy in the neonatal period

Case 1.—Girl, birth weight 4230 g. Uncomplicated delivery. At birth moderately distended abdomen. After 24 hours she became flaccid, gray-cyanotic. Hb 53%, r.b.c. 2,600,000, w.b.c. 10,000, thrombocytes 46,000, S.R. 44. A rounded mass was palpated in the abdomen on the right side. Roentgen examination showed that it occupied the entire right side of the abdomen. Two blood transfusions were given. As a renal tumor was suspected, laparotomy was performed. A mass with a more compact center was found and completely removed. The post-operative course was normal. Examination of the specimen revealed that a normal kidney had been removed, which lay embedded in a larger hemorrhage from the adrenal.

Case 2.—Boy, birth weight 3780 g. Mother nephropathia gravidarum. Induced delivery with prepartan and vacuum extractor. At birth the child behaved normally. On the third day signs of intracranial injury appeared, and at the same time masses were palpated in both kidney regions. The child died on the fifth day. Autopsy revealed, in addition to severe intracranial hemorrhage, bilateral hematomas emanating from the adrenals.

Common to both cases was the ease with which the mass could be palpated. It seems that a general muscular hypotonia exists in these conditions. In hypotonic conditions in the neonatal period in shocked or strongly affected children adrenal apoplexy should be borne in mind. Operation should, of course, not be performed in these cases.

Hilding Wetzenstein: An examination of infants with regard to the pes plano-valgus problem

At the Orthopedic Department in Jönköping, in cooperation with the Obstetric Department, an investigation of 2500 children is being carried out with the aim of

differentiating early symptoms of pes plano-valgus. The intention is to follow the children at one-year intervals from the neonatal period to school age. Pes plano-valgus has been diagnosed in 20% of the children.

Preliminary results.—Among children who in the neonatal period had hyperextensibility of the feet and more than 15° valgidity, 36% showed, at one year of age, signs of pes plano-valgus. Among children who in the neonatal period had hyperextensibility but no valgidity, 19% showed at one year of age signs of pes plano-valgus. Among children who lacked both hyperextensibility and valgidity in the neonatal period, 6% showed at one year of age signs of pes plano-valgus. In order to prevent the occurrence of pes plano-valgus it is proposed that children with evident changes in the feet should as early as during the first weeks of life have their feet fixed by means of plaster splints in maximal plantar flexion until the valgidity and hyperextensibility have disappeared. The treatment is supplemented with night splints in a pes equinal position and shoes with elevated heels.

DISCUSSION.—*Per Selander:* Before starting with arch supports and splints for newborn children one must ask whether there is any evidence that such measures can improve a so-called weak infant foot. On the contrary one asks whether supports and plaster splints do not injure the foot. Such poor feet as are seen in children who have been given supports are hardly ever seen otherwise. Children are never or seldom troubled by the so-called flat foot, but on the other hand they are troubled by feet which have been corrected by violent measures.

S. Hermansson and B. Hall: Two cases of subsepsis allergica Wissler

Case 1.—Boy; sensitive to infection, otherwise healthy. At 3 years of age he began

to run a temperature, rising daily to 40°C, which was not affected by antibiotics. At the same time he had diffuse pains in the extremities and occasionally a rubeola-like exanthema. E.S.R. high, leukocytosis, slight anemia. All other examinations gave normal findings. On ACTH treatment the fever became at first remittent and after some time normal. During the following year he had 4 recurrences with febrile periods of about 10 days; in addition joint pains have developed. Occasional exanthema. Moderate elevation of E.S.R. Period of observation approximately 1½ years.

Case 2.—Girl; sensitive to infection, otherwise healthy. Became ill at 11 years of age with pains in several joints and fever, rising daily to 39°, which was not affected by antibiotics. At the same time there was a pruritic rash on the arms and face. E.S.R. high, leukocytosis, slight anemia. All other examinations gave normal findings. Since then one-week periods with fluctuating temperature up to 40°C with a strong feeling of indisposition. Joint pains and slight joint swelling, exanthema. For a period of 1½ years she was largely symptom-free; thereafter she became ill again with fever, exanthema of urticaria type, increasing joint changes of

polyarthritic type, high S.R., leukocytosis. The general condition during the afebrile periods has been strikingly good. No noticeable effect of antibiotics, salicylates, ACTH, Cortisone, Cloroquine; on the other hand some effect from blood transfusions. Period of observation approximately 3 years. The condition is somewhat similar to Still's disease and to so-called periodic disease.

B. Hall: Reactions and complications in triple vaccination

Of 92 mothers whose children had been triple-vaccinated 15 discontinued the vaccination and 18 others stated that the children had had considerable trouble. The most common symptoms were fever, tenderness, and screaming. Abscess formation occurred twice. The reactions appear to be most common after the second injection. One child, according to all signs mentally alert, became apathetic after the first injection at 6 months of age. After the second and third injection he exhibited a severe brain injury. One mongoloid child developed fits the day after the second injection, and these have recurred since then.

Per Selander, Malmö

BOOK REVIEWS

Advances in Tuberculosis Research. *Birkhäuser, H., Bloch, H. and Canetti, G.*

S. Karger, Basel, 1958. 328 pages, 69 figs. 30 tables. Price. SFr. 64.

In this volume Esmund Long has contributed a short review of the progress in tuberculosis research during the last 70 years from the United States point of view; Yamamura has studied the pathogenesis of cavity formation in the lungs of guinea pigs; Pusik & Uvarova demonstrate morphological reactions of the central nervous system in tuberculous patients; Zettergren, after careful histological examination of lymphnodes showing tuberculoid lesions, draws the conclusion that benign lymphogranulomatosis (sarcoidosis) is a tuberculous disease; Wagner discusses the methods of testing anti-tuberculous drugs in mice; Kreis reports studies on enzymatic deficiencies in the isoniazide-resistant tubercle bacilli; Sternberg reviews our present knowledge of and experience with the use of isotopes in the study of experimental tuberculosis. This volume is a true international enterprise, the six articles being written by authors from six different countries in Europe and overseas and presents facts about many topical problems of tuberculosis.

Young Children in Hospital. *James Robertson.*

Tavistock Publications Ltd., London, 1958. 103 pages. Price 4s. 6d.

The author, a psychiatric social worker and psychoanalyst, has for 10 years been engaged in the work of The Child Development Research Unit sponsored by the Tavistock Institute of Human Relations. The object was to study the effects of the loss of maternal care in the first 4 years of life upon

the development of the total personality of the child. The present book is essentially a memorandum written by the author for submission to the Ministry of Health. There is a strong trend in Children's Hospitals today towards humanizing the care of young patients. Since hospitalization puts the emotional well-being of the young child at risk, it is essential that a principle of mental health be accepted as having equal validity and applicability with the principle of asepsis already systematically invoked to safeguard the physical health. The author suggests and illustrates some of the implications for the non-medical aspects of hospital practice. He describes the three stages in the development of the mental reaction of the young child to long-term hospitalization: protest, despair and denial. The last stage is a danger signal; because the child cannot tolerate the intensity of distress, he begins to make the best of the situation by repressing his feelings for his mother. Superficially he may seem happy, well adjusted and settled; he will cease taking the risk of investing love and dependence in anyone, he will no longer be upset when mother and nurses change or leave, because no one matters to him. This final stage of adaptation may be reached in some months or a year or so after separation from the mother. The aftermath of a lengthy stay in hospital in the early years is commonly an extended period of serious maladaptation and unhappiness for the child, and serious difficulties for the family to whose care he is returned. These behaviour disturbances may last for several months, sometimes for a year or more after discharge from hospital. Although fewer young children than was at one time believed develop psychopathic or affectionless characters because of severe deprivation due to long periods in hospital, there is no doubt that some children in their

personality development suffer great damage and others lesser damage from a separation experience. It is a mistake to regard daily visits as the goal of reform. It will not provide adequate contact between the young child and his mother and remains associated with much stress and anxiety. During visits the parents should be free to do much of the ordinary care of the child, subject to overriding medical considerations. The child should have its favorite toy, and an object, which it knows the mother values and will return for, such as a glove, can be left. Each nurse (student nurse) should have a small group of children assigned to her; she should attend to all aspects of body care to each one of her patients. The nursing should be so organized that on off-days and at off-times only one or two known nurses act as relief. The student nurse should not move to another ward until her group of children has been discharged; this would be a rather difficult principle to follow for the Rectors of our nursing schools in devising the training schedule of the pupil nurses. The principal task of preparing the child for hospitalization is difficult; sometimes, in children under 3 and in emergency admissions, it is impossible. Preparation should start about one week before admission, should be simple and trustful, but not more than the child can assimilate. The aim should be to give an honest picture of the strange environment into which the child has to go, and to give reassurance that he will return home.

All doctors, nurses and those concerned with hospital administration, and members of the public who have the responsibility for the care of children in hospital and the happiness of children, should read this excellent book.

Advances in Pediatrics. Vol. X. S. Z. Levine.

Year Book Publishers, Chicago, 1958. 362 pages with numerous tables and illustrations. Price \$9.

This volume of the well-known periodical book contains 7 excellent articles of pediatric

interest by American and Swedish (B. Vahlquist) authors, each one outstanding in his or her field of research. The articles are of the usual high standard that we are accustomed to in the *Advances*. If any of the chapters should be singled out for special mention it should be the first one, written by Barbara Maria Korsch on psychological principles in pediatric practice, which contents should be carefully studied and recommendations applied by every pediatrician in his every-day activities. The other subjects that the Editor has chosen are: treatment of tuberculosis, convulsive disorders, polio-vaccination, staphylococcal infection in newborns, muscular diseases, and the antibody transfer through the placenta.

John A. Hutch: The Ureterovesical Junction.

178 pages. 96 figures. Price \$7.50.

The author, clinical instructor in urology, University of California, is well known from earlier publications on the same subject. He gives a detailed description of the vesicoureteral junction and discusses the etiology and treatment of reflux, especially in the neurogenic bladders. The book is mainly of interest to the urologists.

N. O. Ericsson

Urology in Childhood. D. Innes Williams.

Springer Verlag, Göttingen. 353 pages, 162 figures. Price 159.30 Sw. Cr.

This is the fifteenth volume of the *Encyclopedia of Urology*, edited by Alken, Dix, Weyrauch and Wildbolz. It gives an extremely good and complete presentation of the problems and is refreshingly free of platitudes. Because of the author's wide personal experience his individual opinions and criticisms of certain controversial subjects are quite beneficial. The book has very good illustrations and is well written. It is heartily recommended to anyone interested in the subject of pediatric urology.

N. O. Ericsson

Principal Infectious Diseases of Childhood.
Nelles Silverthorne.

University of Toronto Press 1958. 112 pages.
\$ 3.50.

Dr. Silverthorne who is Senior Physician at the Hospital for Sick Children in Toronto, and Associate Professor of Paediatrics at the University of Toronto, has intended this concise but complete volume primarily for the use of medical students and general practitioners. Compact in its format, and easily read, it will make a useful and valuable addition to any medical library. There are headings: Infections in the newborn, infectious or communicable diseases (which includes the exanthematous illnesses), infections of the nervous system, virus diseases, and respiratory infections. The material is well systematized, and each subsection is followed by a brief paragraph outlining the principles of treatment of the particular disease in question. Particular mention should be made of the section dealing with infections in the newborn period. This rather large area is admirably well condensed, and the important points in diagnosis and management are forcefully brought out. Although not intended as a textbook it should prove exceedingly useful as a guide to the physician who daily sees the conditions which comprise its contents.

Leo Stern, Stockholm

C. Bodechtel: Differentialdiagnose neurologischer Krankheitsbilder

Georg Thieme Verlag. Stuttgart, 1958. 975 pp. and 532 figures. Price 120 DM.

Although this book mostly treats of nervous diseases in the adult, the pediatrician will find in it much valuable information of interest to him. This is particularly true of the infectious disorders in the central nervous system and their differential diagnosis. The interesting statement is made that individual cases of Economo's disease (encephalitis

lethargica) have re-appeared after the second world war. An instructive discussion is presented about the differential diagnosis between dissimilar progressive brain diseases, and the same holds true of the differential diagnosis between subdural hematoma and brain tumor. Much information of value to the pediatrician is presented in the chapter on metabolic disorders in the central nervous system, on account of the occurrence of such disturbances especially in childhood (Fölling's disease, familial diffuse sclerosis in its different manifestations, Tay-Sach's disease, Gargoylism, Gaucher's disease etc.). The difficulties are stressed of differentiating in the beginning between Oppenheim's syndrome (myatonia congenita) and Werdnig-Hoffmann's disease. The former disease is also discussed in another chapter devoted to muscular diseases. Myatonia congenita is considered to be an independent disease having a good prognosis, and caused by a faulty differentiation of the motor end-plate. The same chapter treats extensively of the different myodystrophies in children and adults. The chapter on deformities and disease processes caused by malformations is of course of greatest interest to the pediatrician. This also includes Recklinghausen's disease, which is particularly difficult from a differential diagnostic point of view because of its highly variable manifestations and clinical course. A separate chapter treats of exogenous and endogenous states of intoxication in the central nervous system. Many of the reported cases of nervous diseases used as examples comprise children, and numerous photographs are taken of children. The book contains a rich array of excellent schematic drawings and satisfactorily reproduced photographs of typical cases affected with the disease. The general index lists nearly 4000 words, which greatly facilitates finding the desired information without loss of time. This book is warmly recommended also to pediatricians and libraries in pediatric hospitals as a valuable reference volume.

ANNOUNCEMENT

IX International Congress of Paediatrics

The IX International Congress of Paediatrics is taking place from July 19-25, 1959 under the patronage of Her Majesty The Queen.

The Scientific Program is designed to follow the chronology of childhood, starting with the cell and progressing through to adolescence, each subject being developed through initial Plenary Sessions leading to Panel and Round Table discussions. Scientific Exhibits, of which an extraordinary number have already been submitted, will be selected to complement the scientific sessions. The Congress Committee is sparing no effort to make the Scientific Program an outstanding educational achievement. Participants in the Program will be those who have proven themselves to be outstanding workers in each field, and will be drawn from all corners of the globe. Friday after-

noon (July 24) is being reserved for three addresses of particular significance.

Postgraduate students, introduced by their Department Heads, are welcome to attend the Congress at the reduced registration fee of \$20.00 (the deadline for which is April 30, 1959).

A social and recreational program has been planned for wives of delegates as well as older children. The younger ones will have their own program of games and events, under the watchful eyes of qualified supervisors.

All registration should be in by January 31, 1959. If you wish further information do not hesitate to get in touch with the Secretary General, P.O. Box 215 Westmount, Montreal 6, Canada.

From the Neonatal Department of the 1st Municipal Hospital of Brno (Head: Anna Poje-
rová, M.D.) and the 3rd Internal Clinic of Masaryk University (Head: Professor Jaroslav
Pojer, M.D., Ph.D.), Brno, Czechoslovakia

On Enzymatic Activity in the Neonatal Period

by ANNA POJEROVÁ and JOSEF TOVÁREK

The significance of serum transaminases is a wellknown fact. The best known are glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT), whose diagnostic value has frequently been emphasized in world literature.

The significance of aldolase (ALD) is also widely familiar.

The named enzymes are present in human tissues of various organs. GOT is present mostly in the heart muscle, liver, skeletal muscles, and shows a gradual decrease in regard to the kidneys, spleen, lungs and pancreas (21). GPT is present in the liver in a greater amount than in other organs. Like all enzymes of fermentation, ALD is present practically in all cells. A higher concentration of it was found in cells with higher carbohydrate metabolism, chiefly in the skeletal muscles (20). The values of all these enzymes in the blood serum are small. Their level rises if the barrier between the cell and the circulation is interrupted. The experimental necrosis of the heart muscle in animals was followed by a raised value of GOT in the serum (21). Through the study of the activity of these enzymes in the serum, of their alterations and mutual combinations, laboratory differential diagnosis of the disease state is fulfilled (myocardial infarction, infarction of the lungs, hepatitis, liver cirrhosis, metastatic infiltration, muscle dystrophias, myositis (21, 13, 12).

We set ourselves the task of investigating GOT and GPT as well as ALD in the blood serum in early neonatal period, and of studying the connection between these values and the values in the umbilical blood serum.

Method

The transaminases were determined spectrophotometrically according to Reitman & Frankel (14). We used a Koutský K 56 spectrophotometer of 505 m μ transparency. The results are expressed in mM glutamic acid/1 ml/1 hr.

Aldolase was measured photometrically by Sibley & Lehninger's method (16), a photometer Klett-Summerson with a green filter (540 m μ) being employed. The results are given in extinction values multiplied by 1000.

Patient Material

The activity of GOT in the serum (SGOT), GPT in the serum (SGPT) and ALD in the serum (SALD) was determined:

1. In the serum of the cord blood (both arterial and venous) in 32 specimens. The blood was obtained immediately after the separation of the child from the placenta; it was taken from the placental stump of the cord by free flow before the expulsion of the placenta.

Careful manipulation is necessary during this procedure. Pressing the cord might cause

an intermixture of Warton's jelly and of the fluid from the squeezed walls of the blood vessels to appear in the examined material. Under these circumstances the values of the enzymes more or less alter.

2. In 66 specimens of the blood serum of infants of from 2 hrs 40 min to 61 days. In the first group there were 49 specimens taken from newborn infants varying in age from 2 hrs 40 min to 7 days; in the second, 17 specimens taken from infants varying in age from 9 to 61 days.

The blood was taken from the cubital vein. We carefully avoided any action that might traumatise the tissue and cause an intermixture of tissue fluid in the taken sample. The blood for the investigation of the three enzymes was all taken at one time, in some cases also for the determination of the bilirubin level in the blood (according to Jendrassik-Gróf).

In 14 cases the determination of enzymes was repeated, though not at equal intervals, throughout the first two months of life. (As they were usually released on or soon after the seventh day, the infants were seldom available for the blood specimens to be taken from them.) In 11 newborn infants the values of enzymes in the serum of the blood from the cord, and of those in the serum from the blood of newborn infants during the first days of life, were collected. In one case, we got 1 specimen from the cord blood and 2 specimens from the blood during the first days of life.

After coagulation the serum was separated and stored in a refrigerator. Estimations were made as soon as possible. Hemolysed blood was carefully removed.

All the newborn infants covered by this study were mature and varied in birth weight from 2350 g to 4750 g. The postnatal course was uneventful. Cases were chosen at random without any consideration of the degree of jaundice. On the whole the activity of the three determined enzymes were measured in 98 specimens of blood, taken from 71 infants varying in age from birth (0 day, cord blood) to 61 days.

Results

In *Table 1* are shown the results of the activity of the determined enzymes in the serum of the cord blood of 32 specimens. The activity of SGOT varied between 0.3 and 3.40, the range of SGPT being on the contrary lower (0.3-1.20). The activity of SALD had as its lowest value 105 and as its highest 1450. According to our results this high value was rather unusual, for all the other values were markedly lower; the second highest value in our table is merely half this value. We found this highest value in a case which at the same time showed the highest value in SGOT. A study of the postnatal course of this infant suggested no explanation of these high values. According to our investigation it is possible to look upon a vacillation between 105 and 780 for SALD in the cord blood as normal.

In *Table 2* are noted the values of 66 specimens taken from children aged from 2 hrs 40 min to 61 days. The range of values for SGOT in the first 7 days of life is 0.8-4.8 with the maximum on the 4th day of life. For SGPT the range is 0.3-2.7 with a maximum on the 5th day of life. In SALD the range is 170-1100 during the first week of neonatal life. We found the maximum on the 2nd day of life.

We saw no connection whatever between the level of bilirubin and the values of the investigated enzymes: in Case 23, SGOT 4.3, SGPT 2.5, SALD 800, bil. 7.6 mg %; in Case 26, SGOT 2.42, SGPT 1.1, SALD 920, bil. 5.7 mg %. On the contrary, the enzyme values, which were like in Cases 23 and 26, high (SGOT 3.2, SGPT 2.7, ALD 700 in Case 37), were in connection with the value of bilirubin 22.8 mg %.

TABLE 1. Activity of glutamic oxaloacetic transaminase (SGOT), of glutamic pyruvic transaminase (SGPT), and of aldolase (SALD) in 32 specimens of cord blood-serum.

Transaminases are expressed in mM glutamic acid/1 ml/1 hr. SALD is given in extinction values multiplied by 1000.

Case No.	SGOT	SGPT	SALD	Case No.	SGOT	SGPT	SALD
1	1.0	0.3	680	17	0.7	0.3	115
2	2.8	0.4	540	18	1.2	0.7	320
3	0.5	0.8	205	19	1.2	0.7	300
4	1.7	0.8	450	20	1.4	1.0	250
5	1.7	0.7	780	21	0.8	0.7	105
6	2.4	0.25	700	22	1.4	1.1	620
7	1.1	0.4	520	23	1.0	1.2	180
8	0.6	0.85	165	24	0.8	0.5	280
9	0.6	0.2	360	25	1.3	0.8	270
10	1.5	0.5	235	26	1.3	1.1	700
11	0.6	0.4	320	27	1.2	0.7	520
12	0.9	0.4	380	28	1.2	0.8	360
13	3.4	0.9	1,450	29	1.1	0.7	330
14	1.2	0.6	255	30	1.45	0.7	260
15	0.4	0.6	120	31	0.3	0.4	195
16	0.6	0.4	305	32	1.1	1.0	300

Fig. 1 captures the values of the activity of the estimated enzymes from the cord blood and from the blood of infants from the first day of life till the end of the 2nd month. In those cases from which 2 specimens from the blood of a newborn infant in an earlier or later period of life and from its cord blood were taken or from the blood of newborn infants taken twice at irregular intervals a connecting line is drawn.

(a) SGOT reached a peak on the 4th day of life and then sank. The graph shows how the activity of SGOT grows from the value of the cord blood up to that of the blood of the newborn.

(b) SGPT behaves in the same way as SGOT reaching its peak on the 5th day of age.

(c) Like the levels of SGOT and SGPT, the level of SALD rises after birth; its growth, however, is not so striking as in transaminases. In 2 of our cases it even sank. In the graph it is to be seen that the

sinking of SALD is even steeper towards the end of the 2nd month of life than in the graph of transaminases.

The horizontal slightly dotted stripe shows normal values for adults. Our determination discloses the fact that in the first week of life the great majority of activity values of SGOT and SALD are higher than in normal adults.

Discussion

We propose to compare our results with those found in healthy adults and in women 24 hrs before the end of labour.

Adults

	μ	σ	Range
SGOT (62) ^a	0.53	± 0.18	0.25-0.95
SGPT (55)	0.41	± 0.2	0.15-0.95
SALD (62)	83	± 35.6	35-165

Women, 24 hrs before the birth of the child

SGOT (30)	0.89	± 0.33	0.2-2.2
SGPT (20)	0.46	± 0.35	0.2-1.0
SALD (20)	176.3	± 28.53	70-350

^a Number of specimens in parentheses.

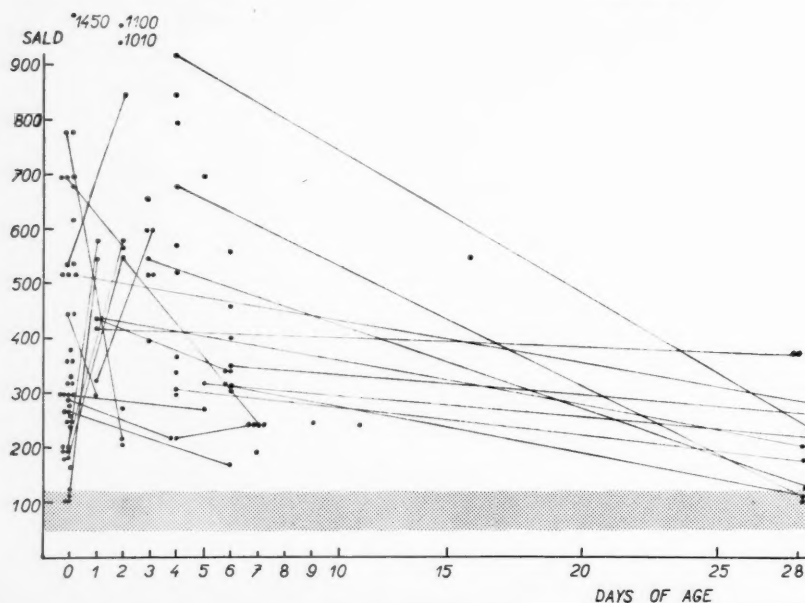
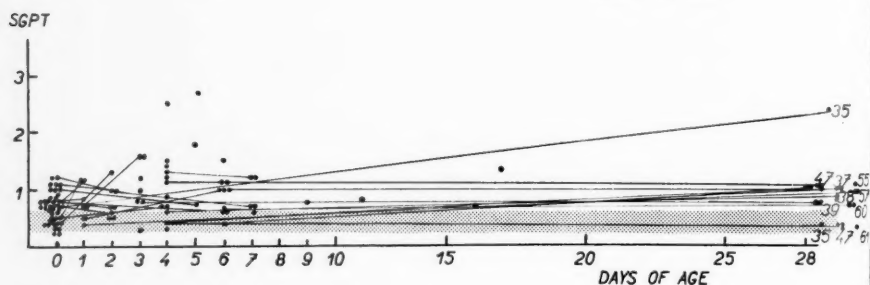
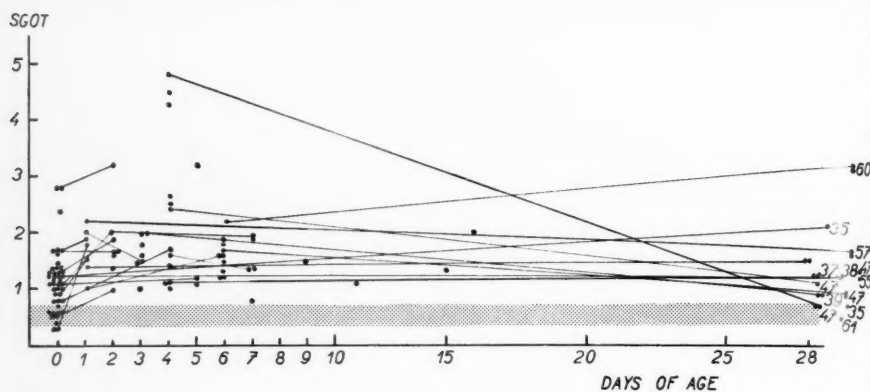


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child.

TABLE 2. Activity of glutamic oxaloacetic transaminase (SGOT), of glutamic pyruvic transaminase (SGPT), and of aldolase (SALO) in 66 specimens of blood-serum of children from birth to the age of 61 days.

Transaminases are expressed in mM glutamic acid/1 ml/1 hr. SALD is given in extinction values multiplied by 1000.

Case No.	Age of infant ^a	SGOT	SGPT	ALD	Bil.	Case No.	Age of infant ^a	SGOT	SGPT	ALD	Bil.
1	2.40	1.0	0.5	440		35	5	1.1	1.8	320	7.4
2	4.45	2.0	0.7	325	3.4	36	5	1.2	0.7	270	10.4
3	11.00	1.9	0.8	300		37	5	3.2	2.7	700	22.8
4	12.00	1.5	1.2	550	9.6	38	6	1.9	1.5	460	5.3
5	21.00	1.8	1.2	580		39	6	2.2	0.65	305	0.9
6	24.00	2.2	0.7	440	12.00	40	6	1.7	1.0	310	
7	24.00	1.4	0.4	420	3.2	41	6	1.2	0.4	350	1.92
8	2	2.0	1.0	550		42	6	1.5	1.1	560	9.4
9	2	1.7	0.6	220		43	6	1.8	1.1	320	3.6
10	2	1.6	0.5	210	9.2	44	6	1.6	1.0	340	8.6
11	2	1.7	0.5	1100		45	6	1.2	0.5	170	2.1
12	2	1.9	1.9	570		46	6	1.3	0.6	400	1.00
13	2	3.2	1.3	850	14.0	47	7	1.4	1.2	240	
14	2	0.95	0.7	580		48	7	0.8	0.6	190	
15	2	1.4	0.7	275		49	7	1.95	0.7	240	
16	2	1.85	1.85	1010		50	9	1.5	0.75	245	
17	3	1.8	0.3	660	3.4	51	11	1.1	0.8	240	11.2
18	3	1.6	0.8	520	3.0	52	15	1.32	0.7	850	
19	3	2.0	0.8	550	2.5	53	16	2.0	1.3	550	
20	3	1.5	1.6	600	5.6	54	28	1.5	1.0	370	
21	3	1.0	1.0	520	14.0	55	35	0.7	0.3	125	
22	3	2.0	1.2	400	11.8	56	35	2.1	2.4	270	
23	4	4.3	2.5	800	7.6	57	37	1.2	1.0	260	
24	4	4.5	1.4	525	1.6	58	38	1.2	0.8	175	
25	4	1.1	0.6	310	1.88	59	39	0.9	0.7	125	
26	4	2.42	1.1	920	5.7	60	47	0.7	0.3	100	
27	4	4.8	0.4	680	4.4	61	47	0.9	0.9	110	
28	4	1.1	0.3	300	4.8	62	47	1.2	1.0	260	
29	4	2.5	0.85	575	23.4	63	55	1.2	1.0	175	
30	4	1.0	0.7	370	1.9	64	57	1.6	0.9	200	
31	4	2.6	1.5	850		65	60	3.2	0.7	200	
32	4	1.4	1.2	340	8.4	66	61	0.5	0.3	200	
33	4	1.6	1.3	220	8.0						
34	4	1.7	0.7	220	11.2						

^a 2.40 = 2 hrs 40 min.

4.45 = 4 hrs 45 min, etc.

2 = 2 days = 24 to 48 hrs.

3 = 3 days = 48 to 72 hrs, etc.

Fig. 2. Activity of transaminases, glutamic oxaloacetic (SGOT), glutamic pyruvic (SGPT) and aldolase (SALO) in 98 specimens of blood serum, taken from 71 infants varying in age from birth (0 day, cord blood) to 61 days. A connecting line is drawn between specimens taken from one and the same child. Transaminases are expressed in mM glutamic acid/1 ml/hr. SALD is given in extinction values multiplied by 1000. The horizontal slightly dotted stripe shows normal values for adults.)

(Women before and during labour have been brought together under one heading. This estimation is described in detail in another paper.)

In statistical evaluation Student's *t*-test was used. The characteristic *t* was counted and compared with critic values found in tables.

(1) The difference between the activity of SGOT and that of SGPT of the cord blood is not significant in comparison with the blood values of pregnant women 24 hours before the end of labour ($t_{0.01} > t < t_{0.05}$ for SGOT, $t_{0.01} > t > t_{0.05}$ for SGPT). SALD differs significantly ($t > t_{0.01}$).

(2) The differences between values of the cord blood, and the values in newborn infants blood during the first week of life, are statistically significant for both the transaminases ($t > t_{0.01}$), but they are insignificant ($t < t_{0.05}$) for SALD.

(3) The comparison of the values in the first week of life of infants with the values found in the 2nd month of life shows a significant difference for SGOT and SALD ($t > t_{0.01}$), while for SGPT it does not ($t < t_{0.05}$).

(4) The enzyme activity in the first week of life significantly differs from that found in adults ($t > t_{0.01}$).

We did not find any relationship either to the level of bilirubin, or to the weight of the child. We did not even see any connection between the individual values of the investigated enzymes.

SGOT and SGPT in neonatal age were systematically studied by S. Kove, S. Goldstein & F. Wróblewski (8, 9). In the cord blood our values for SGOT are higher, but in the first seven days of life they

equal, in all three enzymes, those of the three mentioned authors. In comparison with the values of Santoni (15), who only evaluated SGOT in the cord blood and in the blood of the newborn on the 4th and 5th days of life, our values are higher too. Abelson brings no numerical results in his report (1).¹

The differences between the values of enzyme activity as established for the neonatal period on the one hand and those established for adult life on the other probably have many reasons. They cannot be sought for only in the various conditions of environment (temperature, oxygen concentration, ion concentration), in the presence of vitamins in different concentration and in the presence of hormones specific for this period, and in the various qualities and quantities of the substratum of enzyme activity (3, 7, 11, 17, 18, 19). We know well how different protein metabolism in the fetus and in the newborn is. The economy of aminoacids, their excretion and determination, the balance of their appearance from the fetal to a late age of the infant, are proof of it (4, 17, 18, 19). The same applies to the economy of carbohydrates. The change of pyruvic acid in the blood, which sinks on the 4th day of life to the values of adults, are a further proof of the discussed difference (6, 17). The chief source of energy in the fetal period are carbohydrates; the newborn, however, very soon exchanges them for fats which it has collected during the fetal period probably partly by way of the placenta. Lipids in the blood of the newborn, though doubled during the first week of life, do not reach the values found in adults (17).

An analysis of the metabolic processes in the umbilical blood shows fetal metabolism. At the same time, however, the excretive activity of the fetus, the diffusion of certain substances from the maternal organism over the placenta to the child, and the activity of the placenta itself, are reflected in it (17).

¹ The values given by Kove *et al.* and Santoni were established by Karmen method, *Sigma Tech Bull.* No. 505; 40 Karmen units = 1.5 mM glutamic acid.

The preponderance of the anaerobic metabolism of carbohydrates over the aerobic ones with all its consequences is one of the characteristic signs of the early postnatal period both in the premature and in the full term infants (17).

The newborn has 5-10% more water than the adult. The younger the fetuses, the more water their tissues contain. There is a different relation of extracellular fluid to intracellular fluid (5, 17). The transfer of water according to the mineral content of the tissues presupposes a change in the permeability of the cells. Bessau expressed this idea in the following way: The newborn reveals an abnormally high permeability, which probably has its significance in fetal metabolism. Here, where the child receives everything by way of the blood not the mouth, thick walls would be an unnecessary and unreasonable hindrance to metabolism and the processes of growth. The newborn is obviously in a transitory stage (5, 2).

In a certain sense, the imbalance of hormones of placental and transplacental origin in fetal and probably in earliest postnatal life influences the permeability of cellular membranes (3). This period of life is characterised by all the mentioned physiological peculiarities, going hand in hand with functional immaturity, with abnormal growth in the intrauterine and extrauterine phases, as well as with the adaptation to extrauterine life (10, 17).

A markedly changed cell permeability is one of the most characteristic features of

the fetal and early postnatal periods; it is therefore understandable that together with a number of diverse circumstances, it has proved highly relevant to the problems dealt with in the present paper. Our results show that adaptation is very individual and that this period of human life shows great variations.

In the differential diagnosis of jaundice of unknown origin in the neonatal period, the systematic investigation of the levels of SGOT and SGPT has been found to be of great benefit. Both the transaminases are continually raised in atresia of the bile ducts and transitorily in "inspissated bile syndrome". The activity of SGOT is temporarily raised in a very severe hemolytic disease of the newborn (8).

A systematic investigation of all three enzymes in pathological states of the newborn will doubtlessly be a benefit to differential diagnosis for this period of life in the sense of "battery tests".

Acknowledgement

The assistance of Mrs. Anna Gerylovová, graduated mathematician, of the Institute for the Theory and Organisation of Health Service (head: Assistant Professor Adolf Žáček), in carrying out the statistical evaluation is gratefully acknowledged.

Summary

The activity of glutamic oxaloacetic transaminase in the serum (SGOT) and glutamic pyruvic transaminase in the serum (SGPT) according to Reitman & Frankel and aldolase in the serum (SALD) according to Sibley & Lehninger was simultaneously determined in 98 specimens of blood serum from 71 infants.

Thirty-two specimens were of cord blood, 49 of newborn infants of from 2 hrs 40 min to 7 days of age, 17 of newborn infants of from 9 to 61 days of age. In 14 cases the investigation was carried out twice during the first two months of life. In 11 infants values were gained for cord blood and for blood taken in the first days of life. In 1 case,

1 specimen was obtained from cord blood and 2 from blood during the first days of age.

All the infants were mature and healthy. No relation to the infant's weight, the bilirubin level in the blood, nor any mutual connection between the investigated enzymes were found.

In the cord blood were found the following ranges of activity: SGOT, 0.3–3.40; SGPT, 0.3–1.2; SALD, 105–780. (The transaminases values are expressed in mM glutamic acid/1 ml/1 hr, the aldolase values in the extinction values multiplied by 1000.) This grade is found normal for cord blood.

In the blood of the newborn from the first 7 days of life we found a range of activity SGOT from 0.8 to 4.8 (maximum on the 4th day of life), SGPT 0.3–2.7 (maximum on the 5th day of life), SALD 170–1100 (maximum on the 2nd day of life).

The values of SGOT, SGPT and SALD are in the neonatal period significantly higher than those found in normal adults.

A systematic investigation of all the three enzymes in pathological conditions of the newborn will doubtlessly be of distinct diagnostic value for this period of life.

A propos de l'activité des enzymes chez le nouveau-né.

L'auteur a procédé à des déterminations simultanées de l'activité de la transaminase glutamique oxalo-acétique dans le sérum (TGOS) et de la transaminase glutamique pyruvique dans le sérum (TGPS) d'après la méthode de Reitman et Frankel ainsi que de celle de l'aldolase du sérum (ALDS) d'après la méthode de Sibley et Lehninger sur 98 échantillons de sérum sanguin provenant de 71 nouveau-nés. Trente-deux de ces échantillons provenaient du cordon; quarante-neuf autres avaient été prélevés sur des nouveau-nés âgés d'un à sept jours et les dix-sept derniers provenaient de nouveau-nés âgés de neuf à soixante et un jours. Dans quatorze cas, ces dosages furent effectués deux fois au cours des deux premiers mois de la vie. Pour onze bébés, ces dosages furent effectués sur du sang du cordon, puis sur du sang prélevé au cours des premiers jours qui suivirent la naissance. Dans un cas, un échantillon fut prélevé du sang du cordon et deux autres échantillons furent prélevés du sang du bébé au cours des premiers jours qui suivirent la naissance. Tous ces bébés étaient nés à terme et étaient en bonne santé. Aucune corrélation avec le poids de l'enfant, avec le taux de la bilirubine dans le sang ou entre les différents enzymes étudiés n'a été constatée. Les taux d'activité trouvés dans le sang du cordon ont été les suivants: TGOS: 0,3–3,4; TGPS: 0,3–1,2; ALDS: 105–780 (les taux des transaminases s'expriment en mM d'acide glutamique par cm³ et par heure; les taux d'aldolase équivalent aux valeurs d'extinction multipliées par 1000). Ces valeurs sont normales pour le sang du cordon. Les valeurs trouvées pour les échantillons de sang prélevés sur des nourrissons âgés d'un à sept jours ont été de 0,8–4,8 (avec un maximum le quatrième jour) pour la TGOS, de 0,3 à 2,7 (avec un maximum le cinquième jour) pour la TGPS et de 170 à 1100 (avec un maximum le deuxième jour) pour l'ALDS. Ces taux de TGOS, de TGPS et d'ALDS trouvés chez le nouveau-né sont nettement inférieurs à ceux que l'on rencontre chez les adultes normaux. Une étude systématique des taux de ces trois enzymes dans les états pathologiques du nouveau-né serait sans aucun doute nettement intéressante au point de vue diagnostique pour cette période de la vie.

Über die Enzymtätigkeit in der Neugeborenenperiode.

Die Aktivität von Serum Glutamin-oxaloacet-transaminase (SGOT) und von Serum Glutamin-pyruvin-transaminase (SGPT) wurde nach der Methode von Reitman und Frankel und von Serum Aldolase (SALD) nach der Methode von Sibley und Lehninger in 98 Proben von Blutserum bei 71 Kindern gleichzeitig bestimmt. Zweiunddreissig Proben waren von Nabelschnurblut, 49 von weniger als 7 Tage alten Neugeborenen und 17 von Säuglingen im Alter von 9–61 Tagen. Bei 14 Fällen wurde die Untersuchung zweimal während der ersten zwei Lebensmonate ausgeführt. Bei 11 Kindern wurden sowohl die Werte für Nabelschnurblut als auch für in den ersten Lebenstagen entnommenes Blut ermittelt. Bei einem Fall wurde eine Probe von Nabelschnurblut und 2 von Blut während der ersten Lebenstage entnommen. Alle Kinder waren reif und gesund. Es fand sich keine Beziehung

zum Körpergewicht der Kinder, zum Bilirubinspiegel im Blut, noch eine gegenseitige Beziehung zwischen den untersuchten Enzymen vor. Die folgenden Aktivitätsbreiten wurden für Nabelschnurblut festgestellt: SGOT 0,3-3,4; SGPT 0,3-1,2; SALD 105-780 (die Transaminasewerte sind in mM Glutaminsäure/1 ml/1 Stunde, die Aldolasewerte in Vernichtungszahlen multipliziert mit 1000 ausgedrückt). Dieser Grad ist als normal für Nabelschnurblut zu betrachten. Im Blut aus den ersten 7 Tagen der Neugeborenen betrug die Aktivitätsbreite 0,8-4,8 (mit einem Maximum am 4. Lebenstag) für SGOT, 0,3-2,7 (mit einem Maximum am 5. Lebenstag) für SGPT und 170-1100 (mit Maximalwert am 2. Lebenstag) für SALD. Die SGOT, SGPT und SALD Werte sind in der Neugeborenenperiode beträchtlich höher als bei normalen Erwachsenen. Systematische Untersuchung auf alle drei Enzyme bei pathologischen Zuständen bei Neugeborenen wird zweifellos entschiedene diagnostische Bedeutung für diesen Lebensabschnitt besitzen.

La actividad enzimática en el periodo neonatal.

Se determinaron simultáneamente la actividad de la glutámico oxalacético transaminasa en suero (SGOT), la glutámico pirúvico transaminasa en suero (SGPT), de acuerdo a Reitman y Frankel, y la actividad de la aldolasa en suero (SALD), de acuerdo a Sibley y Lehninger, en 98 muestras de suero tomadas de 71 lactantes. Treinta y dos de las muestras fueron tomadas del cordón umbilical, 49 de los recién nacidos tenían 7 días de edad, 17 de 9 a 61 días. En 14 casos la investigación fué realizada dos veces durante los 2 primeros meses de edad. En 11 lactantes los valores fueron obtenidos a partir de muestras, de sangre y del cordón, tomadas en los primeros días de vida. En 1 caso, una muestra de sangre del cordón y dos de sangre, fueron obtenidas dentro de los primeros días de vida. Todos eran lactantes sanos, nacidos a término. No se encontró ninguna relación entre el peso de los lactantes, el nivel de bilirubina en sangre, ni tampoco ninguna conexión entre las enzimas investigadas. En la sangre tomada del cordón fueron determinados los siguientes grados de actividad: SGOT: 0,3-2,7, SGPT: 0,3-1,2, SALD: 105-780 (los valores de las transaminasas son expresados en mM ácido glutámico/1 ml/1 hr, los valores de aldolasa en valores de extinción multiplicados por 1000). Estos valores son considerados normales para sangre del cordón umbilical. En la sangre de los recién nacidos dentro de los primeros 7 días de vida, la escala de actividad fué: 0,8-4,8 (máximo en el cuarto día) para SGOT, 0,3-2,7 (máximo en el quinto día) para SGPT y 170-1100 (máximo en el segundo día de vida) para SALD. Los valores de SGOT, SGPT y SALD son en periodo neonatal significativamente más elevados que aquellos hallados en el adulto normal. Una investigación sistemática de estas 3 enzimas en condiciones patológicas del recién nacido, será sin duda de claro valor diagnóstico para este periodo de la vida.

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1st Municipal Hospital
Neonatal Dept.
Brno
Czechoslovakia

Hereditary Pitressin-Resistant Diabetes Insipidus

by I. J. CARRÉ and J. E. MCCOY

Although cases of pitressin-resistant diabetes insipidus had been reported previous to 1945 (2, 17), it was not until the publications of Waring, Kajdi & Tappan (1945) and Forssman (1945) that the existence of a distinct inherited form of pitressin-resistant diabetes insipidus became established.

Subsequent publications have confirmed these initial observations. However, allowing for the recording of individual families in more than one publication by the same or different authors, only 4 pedigrees containing 2 or more affected individuals have since been reported in detail (3, 10, 27, 31). Three additional families with more than one affected member are quoted by Cates & Garrod, Chung & Mantell and West & Kramer. No detailed pedigrees are provided. During the same period 9 other patients have been reported who, though affected with a similar disorder, differed in having either a negative or indefinite family history (3, 7, 10, 14, 16, 19, 21, 22).

We now record a previously unpublished pedigree of pitressin-resistant diabetes insipidus. Also reported are the results of studies carried out on one patient and on the patient's mother and sister who were both free of symptoms.

Case History

D. M., a white male child, was first seen at the Royal Children's Hospital, Melbourne, when 2 years and 10 months of age. His parents were from the U.S.A. and temporarily resident in Australia.

Both the pregnancy and birth were uneventful. He weighed 3390 g at birth. He was initially breast fed but because of fretfulness, a reluctance to feed and occasional vomiting, bottle feeding was introduced at 6 weeks of age. At about this time his mother noted that he remained more contented if given supplements of water in addition to his milk feeds. During the following months his eagerness for large quantities of fluid became more apparent. At 6 months he was drinking up to a litre and a half of water daily in addition to milk feeds. When 10 months old he was investigated in the U.S.A. At that time his 24-hour fluid intake averaged 3,200 ml. The maximum recorded urine specific gravity was 1005. An intravenous pyelogram was reported as showing normal excretory function. His blood urea was 26.5 mg%. His polydipsia and polyuria were unaffected by pitressin. During this period he had an erratically elevated temperature of up to 39°C.

Except for excessive thirst and polyuria his subsequent progress proved satisfactory. At 15 months he weighed 8.8 kg and at 2 years 12.7 kg. His abdomen which had been slightly protuberant from birth became increasingly so as he grew older. Mental development had been perfectly normal.

There was a family history of diabetes insipidus (Fig. 1). Both parents were alive and in good health. The patient's young brother, born subsequent to the present studies on D. M., suffered from a similar complaint but his elder sister was symptom free. Though there is little doubt that both third generation male relatives (III.1 and III.3) suffered from a form of diabetes insipidus there is no available evidence indicating whether or not their condition was in fact resistant to pitressin.

Except for a moderately distended abdomen and a small accessory auricle just anterior to the right ear no abnormal findings were elicited on clinical examination. His blood pressure was 95/65. He weighed 14.2 kg and was 88.9 cm tall. He was mentally bright and intelligent.

Investigations

Blood: haemoglobin was 15.8 g/100 ml. Leucocytes numbered 10,200/cmm of which neutrophils comprised 62%, lymphocytes 28% and monocytes 10%. **Radiographs** of chest, long bones and skull showed no abnormality. **Mantoux** reaction with old Tuberculin 1:1000 was negative.

Urine (examination of random samples). No casts and no excess of either red or white cells were seen and no albumen, sugar or ketone bodies were detected. No amino-aciduria was demonstrated on paper chromatography. The maximum recorded specific gravity was 1002. The pH of the urine was constantly in the neighbourhood of 5.5.

A fluid balance over a period of 48 hours showed an average 24-hour intake of 8.07 litres and an output of 8.10 litres.

Blood chemistry

(a) Initial results were recorded with the patient on an unrestricted fluid intake (Table 1).

(b) The patient was next subjected to a period of fluid deprivation. The test was discontinued after 18½ hours starvation when the serum electrolytes were re-estimated. These showed a hyperelectrolytaemia (Ta-

TABLE 1. *Results of laboratory investigations.*

	With patient on unrestricted oral fluids	After 18½ hours fluid deprivation
<i>Serum</i>		
Sodium (mEq/l)	144	168
Potassium (mEq/l)	4.1	—
Calcium (mEq/l)	5.8	—
Bicarbon. (mEq/l)	21.8	18.2
Chloride (mEq/l)	110.3	133.4
Inorganic phosphate (mEq/l)	3.0	—
Total proteins (mEq/l)	15.9	20.3
Urea (mg/100 ml)	19 and 33	43
Cholesterol (mg/100 ml)	100	—
pH	7.4	—
<i>Blood</i>		
Haematocrit (%)	35	39

ble 1). During the first 2½ hour period of the test he passed 600 ml of urine but only 60 ml during the final 2½ hours. The specific gravity of the latter urine specimen was 1007 and the pH 5.4. Towards the end of the test he became pale, sunken-eyed and listless and presented the typical clinical appearance of severe dehydration. The maximum recorded temperature during the test was 37.2°C.

An *intravenous pyelogram* failed to outline the renal calyces and pelves due to dilution of the dye. The child's fluid intake was not restricted during the carrying out of this investigation.

A *creatinine tolerance test* was performed using an identical procedure to that described by Sundal. 710 mg creatinine were given orally to the fasting patient. The plasma creatinine levels 2 and 6 hours later were 4.3 and 1.4 mg% representing a 67.4% fall within the 4 hours. This is a normal result under the conditions of this test.

Phenolsulphonephthalein test. Following the intramuscular injection of 6 mg of phenolsulphonephthalein, 80% of the injected dye had been excreted in the urine within 3 hours.

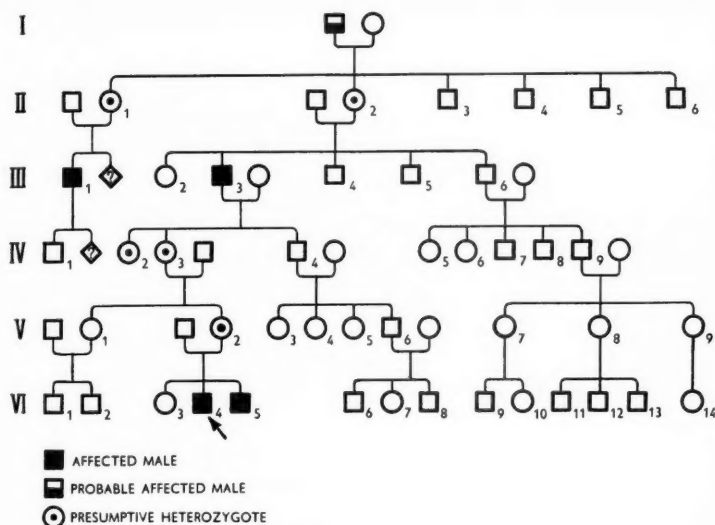


Fig. 1. Pedigree of patient D. M.

On cystoscopy a normal veru montanum and bladder neck were seen; the bladder mucosa was pale and trabeculated. The right ureteric orifice appeared a little larger and more patulous than normal. The left ureteric orifice was a "crevice" in the lateral horn of the trigone; peristaltic activity was visible. Retrograde pyelography showed no abnormality. A micturating cysto-urethrogram demonstrated good voluntary control and no abnormality of the bladder neck or urethra; the bladder was enlarged.

A bone marrow aspiration showed a normal cellular marrow; no cystine crystals were seen.

Slit lamp examination of the cornea demonstrated a normal transparency and no crystals.

Pitressin Tests¹

The patient was given a preliminary skin test with 0.1 unit pitressin. No evidence of undue sensitivity was demonstrated.

Two series of tests were performed. All

¹ A standardised pitressin preparation provided by Parke Davis & Co. Ltd., Sydney, was used in all tests.

urine specimens were obtained by the patient voiding voluntarily.

(a) *Control.* With the patient on an unrestricted fluid intake a loading dose of 600 ml of water was given by mouth. The ingested load was excreted in 142 minutes. The urinary specific gravity remained constant at 1002 to 1003 (Fig. 2A).

(b) *Response to pitressin.* Under identical conditions to the control test, 5 units of pitressin were injected intramuscularly after completion of the water loading. Similar results were obtained; the water load was excreted in 105 minutes and there was no increase in urinary specific gravity (Fig. 2B). Shortly after the injection of pitressin the patient became pale and had a bowel action. There was no complaint of abdominal pain and no vomiting. His blood pressure remained unaltered throughout the test.

Sodium chloride loading test

A further test was carried out in an identical manner to the preceding control test

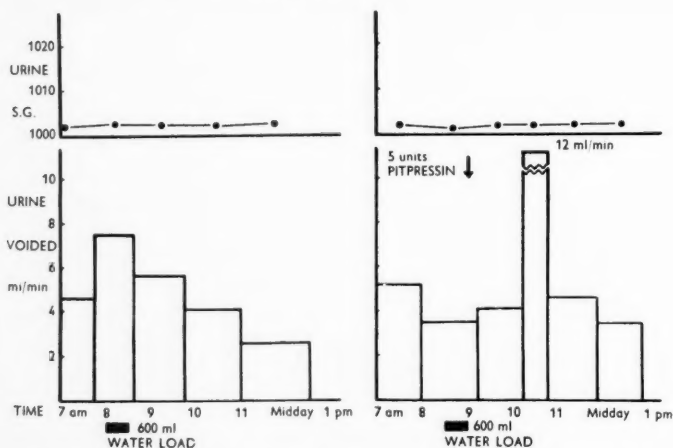


Fig. 2. Effect on rate of urine excretion and specific gravity following the ingestion of a 600 ml water load by patient D. M. A. *A*, Control. *B*, when combined with injection of pitressin. Note: The rapid urine excretion shown in *B* as occurring between 10 and 11 a.m. is almost certainly an artefact due to the child not having completely emptied his bladder at the preceding act of micturition.

but with the substitution of the original water load by 600 ml of a sodium chloride mixture (400 ml of physiological saline and 200 ml orange juice). This ingested fluid load was excreted in 215 minutes; the urinary specific gravity did not exceed 1003. Serum sodium and chloride estimations performed $3\frac{1}{2}$ hours after the ingestion of the saline mixture revealed hyper-electrolytic values (Na 152.8 mEq/l; Cl. 121.4 mEq/l). The test was not repeated with pitressin.

Following the saline load the patient became intensely miserable, pale, cyanosed and very thirsty. At the end of the test he was permitted unrestricted fluids and drank 2½ litres of fluid within 20 minutes.

Serum levels of anti-diuretic hormone. The report on this investigation stated "the activity of the serum with regard to anti-diuretic hormone appears to be within normal limits".

Investigation of Mother and Sister

The patient's mother and elder sister were also investigated. Both were entirely free of symptoms. Urine concentration and pitressin tests were performed.

Mother

Urine concentration test. After 20 hours of fluid deprivation the urine specific gravity was 1024.

Pitressin tests

(a) *Control.* With the subject on a preliminary unrestricted fluid intake she was then given a loading dose of 1500 ml fluid by mouth. The ingested load was excreted within 160 minutes (Fig. 3A).

(b) *Response to pitressin.* Under similar conditions to the control test, 20 units of pitressin were injected after completion of the water loading. After 3 hours little more than 200 ml of urine had been passed, with a maximum recorded urine specific gravity of 1019 (Fig. 3B).

Twenty minutes after the pitressin injection she felt faint, became pale, complained of abdominal cramp, vomited and was incontinent of urine and faeces.

Sister

(Sister 6 years of age.) *Urine concentration test.* After 20 hours of water deprivation a urine specific gravity of 1031 was attained.

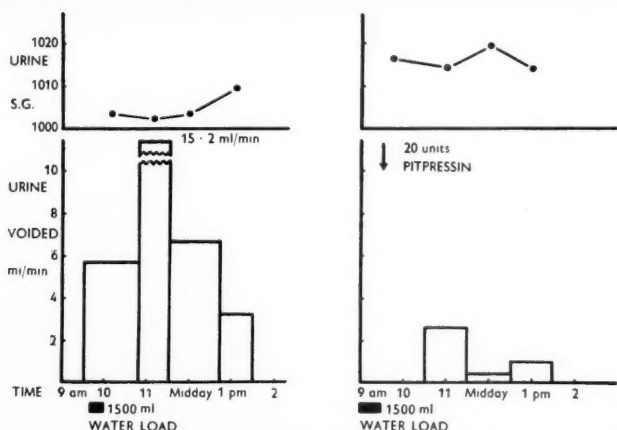


Fig. 3. Effect on rate of urine excretion and specific gravity following the ingestion of a 1500 ml water load by the patient's mother. *A*, Control. *B*, when combined with injection of 20 units pitressin. Note: The urine measurement for the period between 9 and 10.30 a.m. in test *B* was inaccurate due to incontinence precipitated by the pitressin.

Pitressin tests

These tests were performed in a similar manner to those on the patient and the patient's mother.

(a) *Control.* Within 150 minutes of ingesting a water load of 900 ml she had voided 1050 ml of urine.

(b) *Response to pitressin.* Ten units of pitressin were given intramuscularly immediately after the ingestion of a water load of 900 ml. Only 146 ml of urine were passed during the following 3 hours. The maximum urine specific gravity recorded during the test was 1020.

Fifteen minutes after her pitressin injection she reacted by becoming pale and complaining of abdominal cramps.

Treatment

The patient was provided with and encouraged to drink abundant and unrestricted quantities of fluid. No other dietary supplements or restrictions were prescribed.

The regular nightly disturbance of both patient and parents resulting from the child's

frequent and copious nocturnal urinary incontinence proved to be a particularly distressing feature of our patient's illness. In an effort to alleviate this problem the patient was each night fitted with a portable urinal. A "Simplex" Bed Incontinence apparatus¹ was used similar to that originally described by Chapel with certain modifications. The corrugated rubber sheath instead of leading directly into a drainage tube was connected to a rubber bag. A non-return valve was incorporated at its connection with the bag thereby preventing back flow of urine from the apparatus. The bag, which when in use was strapped to the inner aspect of the patient's thigh, then drained directly by a connecting tube into a receptacle under the bed. The use of this apparatus proved eminently satisfactory and ensured 6 dry and undisturbed nights out of every 7.

Discussion

The clinical features of pitressin-resistant diabetes insipidus have been de-

¹ The apparatus was supplied by Medical Supplies Association, 53 Park Royal Road, London, N.W. 10.

scribed in patients suffering from a variety of renal disorders—Lignac-Fanconi Disease (1), chronic pyelonephritis (9, 24), renal polyarteritis nodosa (8), obstructive hydronephrosis (24, 25), and during the recovery phase of acute renal failure (23). It has been suggested that a relationship might exist between hereditary pitressin-resistant diabetes insipidus and Lignac-Fanconi disease (18, 22). No evidence was obtained in our case of any urinary tract obstruction and no renal impairment was demonstrated other than an inability to produce a concentrated urine. Despite specific investigation no abnormalities were found suggesting the co-existence of cystine storage disease.

Instances of pitressin-resistant diabetes insipidus associated with cerebral lesions have also been described. Biggart discussed the necropsy findings in 7 patients with diabetes insipidus associated with anatomical lesions of the hypothalamus. In 3 the condition had proved resistant to therapy with pituitrin and in all 3 the tuber cinereum was found to be involved. By contrast, the nuclei of the tuber cinereum were not demonstrably affected in the other 4 patients whose condition had responded to pituitrin. On the basis of these observations this author suggested that for pituitrin to be effective it may be necessary for the nuclei of the tuber cinereum to be intact.

Two of the reported cases of hereditary pitressin-resistant diabetes insipidus have come to necropsy. In one case, that of Waring *et al.* the only abnormality reported was a mild degree of hydronephrosis. In the patient discussed by Macdonald the spleen contained foam cells similar to those seen in Lignac-Fanconi disease. On micro-dissection of the kidneys the distal tubules and

loops of Henle were reported as appearing "normal in appearance and length". In neither case was any histological abnormality detected in the brain or pituitary gland. Flax & Gersh have reported the results of a renal biopsy on one case. No abnormal findings were noted in either the distal renal tubules or loops of Henle. Thus, no anatomical evidence has yet been produced indicating that the disorder derives primarily from a lesion of the renal tubules.

In patients suffering from hereditary pitressin-resistant diabetes insipidus it is clear that the clinical disturbances arise from a failure on the part of the kidney to produce a concentrated urine. It would seem reasonable to postulate as the basic fault an intrinsic tubular inability to respond to the anti-diuretic hormone in view of the lack of response to pitressin and the fact that the anti-diuretic hormone, in those patients tested, has been demonstrated in normal quantities in both the serum (Macdonald, and present case) and the urine (7, 21). That this hypothesis may not provide a complete explanation is suggested by a particularly interesting patient reported by Wettenhall. In this case normal quantities of anti-diuretic hormone were demonstrated in the serum yet this patient's condition contrary to expectation responded to therapy with pitressin. A somewhat similar though less definite example is afforded by one of Williams & Henry's patients who suffered from hereditary "nephrogenic diabetes insipidus" yet appeared to show a mild response to pituitrin snuff over a period of 4 months. Such cases could possibly be explained by postulating varying degrees of tubular unresponsiveness to anti-diuretic hormone. However, in view of Biggart's observations it is questionable whether

one is justified in regarding the physiological dysfunction as being primarily and solely located in the renal tubule. In the absence of more precise evidence the actual site of the primary defect in such cases must it seems remain in some doubt. For this reason and the fact that a similar clinical syndrome may be produced by acquired renal disorders the descriptive term of hereditary pitressin-resistant diabetes insipidus is preferred to that of nephrogenic diabetes insipidus. Furthermore, it is conceivable that an inter-relationship exists between cases of pitressin-resistant diabetes insipidus on the one hand and cases of diabetes insipidus sensitive to pitressin on the other. Wettenhall's case may afford such a link. In this connection it would be of particular value to ascertain whether the disorder in affected forbears was also invariably equally resistant to therapy with pitressin. The family reported by Haymann & Fanconi would suggest that this may not always be so.

Excluding the present publication the occurrence of similarly affected forbears is recorded in only 4 reported pedigrees. Forssman has extended his originally published pedigree of pitressin-resistant diabetes insipidus (Ellborg & Forssman; Forssman). The pedigree includes 9 affected individuals, all male, in 4 generations. The disorder in all 4 patients tested was shown to be resistant to pitressin. The pedigree reported by Williams & Henry (including the extension by Flax & Gersh) contains 8 affected individuals in 5 generations. All were male and from the information provided the disorder in 4 was definitely resistant to therapy with pitressin. Walker & Rance record a pedigree of 4 generations which includes 4 confirmed cases, all male. Two certain and 2 very probably affected male individuals are included in a family of 4 generations reported by Carter &

Simpkiss. In all 4 pedigrees the mode of inheritance follows a sex linked recessive pattern.

A similar sex linked recessive transmission is clearly demonstrated in our pedigree. Only 4 individuals, all male, are known to have been affected in 5 generations. In two (III.1 and III.3) it is not known for certain whether or not the disorder was responsive to pitressin. It is clear from the pedigree that the 2 sisters, II.1 and II.2, were heterozygous carriers. As their 4 brothers were unaffected it is likely that they had inherited the relevant gene from their father. From II.2 the transmission of the gene through the succeeding generations is readily discernible via an affected male (III.3), 2 heterozygous female carriers (IV.3 and V.2) to the affected patient VI.4 and his brother VI.5. Descended from the 2 unaffected males in generations III and IV (III.6 and IV.4) are 11 females and 10 males all of whom are known to be clinically unaffected, thereby providing additional evidence in favour of a sex linked recessive pattern of inheritance.

It has been reported that an occasional female heterozygous carrier may exhibit mild symptoms of polyuria and polydypsia (3, 30). Furthermore, the observations of Forssman and Carter & Simpkins suggest that it may be possible in some instances to detect the heterozygous state in clinically unaffected females on the basis of an impaired urine concentration test and an inadequate response to pitressin. It was not, however, possible by employing similar tests to detect the heterozygous state in the mother of our patient.

Other than hereditary influences there would appear to be no obvious features of

aetiological importance in these cases. However, it may not be without significance that reported patients tend to have a relatively high birth weight. Of 18 patients whose birth weight has been recorded 17 weighed over 3.15 kg and 7 of these weighed over 3.6 kg at birth (10, 11, 14, 15, 19, 20, 21, 22, 27 and present case).

The provision of an abundant and unrestricted fluid intake is generally acknowledged to be of paramount therapeutic importance not only in preventing dehydration and hyperelectrolytaemia but also in preventing the development of variable degrees of permanent mental defect (10, 15, 20). The normal mental development of our patient may thus be attributable, in at least some measure, to the fact that his parents had on their own initiative provided him with extra fluid supplements from the age of six weeks.

The persistent and copious nocturnal urinary incontinence suffered by these patients inevitably interferes with the

night's rest of both patient and parents whose health may thereby suffer in consequence. Our experience with the use of a portable urinal at night has demonstrated that this measure can be of inestimable benefit and can contribute very materially to the health and well being of both patient and parents.

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Summary

A case is described of a 2 years and 10 months old male child with polydipsia, polyuria and an inability to excrete a concentrated urine. The latter was the only discovered abnormality in renal function. Pitressin was ineffective in alleviating the condition. Symptoms had been present from shortly after birth. From the age of 6 weeks when he was given extra fluid he remained in good health and developed normally both physically and mentally.

There was a family history of the disorder. A pedigree is illustrated showing a total of 4 affected individuals, all male, in 5 generations. The mode of inheritance is consistent with a sex linked recessive transmission.

A satisfactory urine concentrating ability and a normal response to pitressin was demonstrated in both the patient's mother and sister. Neither complained of any symptoms.

The value of a portable urinal at night has been emphasised.

Aetiological and hereditary aspects are discussed and reasons given for preferring the term hereditary pitressin-resistant diabetes insipidus to nephrogenic diabetes insipidus.

Diabète insipide héréditaire résistant à la pitressine.

L'auteur décrit le cas d'un enfant du sexe masculin âgé de 2 ans et 10 mois qui était affligé de polydipsie, de polyurie et d'incapacité d'excréter de l'urine concentrée. Cette incapacité d'éliminer de l'urine concentrée était d'ailleurs la seule anomalie que l'on eût constatée au point de vue de la fonction rénale. La pitressine s'avéra inopérante pour le traitement de cette affection. Les symptômes de cette dernière avaient commencé à se manifester peu après la naissance. A partir de l'âge de six semaines auquel des quantités supplémentaires de liquides lui furent administrées, cet enfant était resté bien portant et s'était développé normalement au point de vue physique comme au point de vue psychique. Il est apparu que plusieurs membres de sa famille avaient souffert de la même maladie. L'arbre généalogique reconstitué pour cinq générations montre que quatre sujets, tous du sexe masculin, en ont été atteints. Le mode de transmission est chaque fois le même avec un caractère récessif lié au sexe. Il a été établi que la mère et la sœur du patient émettaient des urines suffisamment concentrées et réagissaient de façon normale à l'administration de pitressine. Aucune d'entre elles ne se plaignait de troubles quelconques. L'utilisation d'un urinal portatif durant la nuit s'est révélée des plus utile. L'auteur examine ensuite les aspects étiologiques et héréditaires de cette affection et expose les raisons qui lui ont fait préférer la dénomination de diabète insipide héréditaire résistant à la pitressine à celle de diabète insipide néphrogène.

Erblicher pitressinresistenter Diabetes insipidus.

Ein Fall eines 2 Jahre 10 Monate alten Kindes männlichen Geschlechts mit den Erscheinungen von Polydipsie und Polyurie und der Unfähigkeit, konzentrierten Harn auszusecheiden, wird beschrieben. Die letztere war die einzige festgestellte Anomalie der Nierenfunktion. Pitressin war nicht instande, den Zustand zu lindern. Die Symptome waren kurz nach der Geburt aufgetreten. Vom Alter von 6 Wochen aufwärts, wenn zusätzliche Flüssigkeitsmengen zugeführt wurden, verblieb das Kind in gutem Gesundheitszustand und entwickelte sich in körperlicher als auch geistiger Beziehung normal. Die Krankengeschichte wies auf ein familiäres Auftreten der Störung hin. Ein Stammbaum wird angeführt, der insgesamt 4 von der Krankheit betroffene Individuen ausschliesslich männlichen Geschlechts in 5 Generationen aufweist. Der Vererbungsmodus stimmt mit einer geschlechtsgebundenen rezessiven Übertragung überein. Eine zufriedenstellende Harnkonzentrationsfähigkeit und normale Reaktion auf Pitressin wurden sowohl bei der Mutter als auch bei der Schwester des Kranken nachgewiesen. Keine hatte Symptome. Der Wert eines tragbaren Harnbehälters für die Nachtzeit wird unterstrichen. Ätiologische und Vererbungs Gesichtspunkte werden erörtert und die Gründe angegeben, warum die Bezeichnung eines erblichen pitressinresistenten Diabetes insipidus dem nephrogenen Diabetes insipidus vorgezogen wird.

Diabetes insipida pitresin-resistente hereditaria.

Se describe el caso de un niño de 2 años y 10 meses de edad, con polidipsia, poliuria e incapacidad para concentrar sus orinas. Esto último fué la única descubierta anormal en lo que respecta a su función renal. La Pitresina fué inefectiva en mejorar su condición. Los síntomas han estado presentes desde poco después de nacer. Desde las 6 semanas, cuando se le aumentaron sus ingestas líquidas, ha continuado en buen estado y su desarrollo físico y mental ha sido normal. Existe una historia familiar en relación con estos disturbios. El árbol genealógico muestra, en 5 generaciones, un total de 4 individuos afectados, todos del sexo masculino. La modalidad de herencia es compatible con una transmisión regresiva ligada al sexo. La madre y la hermana del paciente mostraron una capacidad de concentración satisfactoria y una respuesta normal a la Pitresina. Tampoco se han quejado de sintomatología de ningún tipo. Se enfatiza el valor de un orinal transportable durante la noche. Los aspectos etiológicos y hereditarios son discutidos, y se fundamenta porque se ha preferido el término Diabetes Insipida Pitresin-resistente Hereditaria al de Diabetes Insipida Nefrógena.

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Dept. of Child Health
Institute of Clinical Science
Grosvenor Road
Belfast, Northern Ireland

From the Pediatric Clinic, University of Gothenburg, and the Central Laboratory, Sahlgren's Hospital, Gothenburg, Sweden

Studies on the Elimination Rate of Bromsulphthalein in Infants and Children

by BERTIL LINDQUIST and LEIF PAULSEN

The liver possesses an amazingly varied amount of biochemical activities which are essential to the proper functioning of the body. It is of course impossible to catch all these mechanisms in one single test. It has been proved, however, that the excretory function of the liver shows a marked sensitivity against damage of the liver parenchyma and that, consequently, a decrease of this function will give informations about the degree of the liver injury.

For a study of the excretory capacity of the liver bromsulphthalein (BSP) seems to be a suitable substance; it may be intravenously injected and it is, at least within a certain time interval (see below) eliminated from the plasma according to an exponential function. As in addition BSP is excreted practically only by the liver, its total clearance will be about the same as its hepatic clearance. Nevertheless the test has not come much into use for clinical routine examinations in pediatric practice.

In the following measurements of the elimination rate of BSP in normal subjects of different age groups are presented. In order to evaluate the technique used in the present investigation as test on liver

function in childhood similar measurements have been performed on proved cases of hepatitis. Finally BSP studies have been applied on a series of newborns with so-called physiologic jaundice.

Short Outline of the Kinetics of Bromsulphthalein

After a rapidly given intravenous injection of a certain dose of BSP a maximum concentration in the blood is reached after 30-45 seconds. If the concentrations of BSP in blood are plotted on a logarithmic coordinate against time on a Cartesian coordinate, it is seen that the process of BSP elimination may be divided into three different phases, each corresponding to a certain interval on the resulting curve (Zimmer, 1956). The *first* phase represents the initial distribution of BSP in the body which has been shown to occur practically only in the plasma compartment. The BSP is quantitatively bound to the serum albumin and mixed in the albumin pool of the blood (Ingelfinger *et al.*, 1948). The duration of this phase is relatively short and varies mainly according to blood volume (body weight) and circulation time; thus in adults it is longer (about 3-4 min.) than in infants (about 2 min.). The *second* phase is exclusively referred to the elimination of BSP from the blood. Corresponding to this phase the plotted values on the curve are

seen to be collected along a straight line within an interval of about 2-4 to 20 minutes after the injection of BSP. Recently it has been shown that at an early state BSP is not completely removed from the circulation by the liver. Using S^{35} -labelled BSP, Brauer *et al.* (1955) found in experiments on dogs with continuous intravenous infusion of BSP that a certain amount was stored in the body carcass, mainly in the skeletal muscles; however, the main proportion—about 80 per cent—could be accounted for in terms of hepatic extraction. Thus in clinical single injection experiments the error in calculations based on the assumption that all of the BSP leaves the circulation via the liver is relatively small. Based on earlier studies with India ink it has been assumed that the excretion of BSP through the liver is mediated by its reticuloendothelial system (see Zimmer, 1956). Later experiments with a carbon-free filtrate of India ink has shown that the increased BSP retention after giving this filtrate probably was caused by a toxic action on the liver cells of a soluble substance in India ink (Shore & Zilversmit, 1954; Zilversmit & Shore, 1954). Radioautographic studies (Krebs & Brauer, 1949) also support the opinion that the uptake of BSP does not involve the Kupffer cells but proceeds directly from the plasma into the hepatic cells. Some observations made by Brauer *et al.* (1955) establish the fact that BSP then undergoes some sort of metabolic transformation before being excreted into the bile. The third phase appear on the semilog plot at an interval of about 20 minutes after injection as a departure on the curve, corresponding to a decrease in the elimination rate of BSP. The cause of this phase is mainly unknown although there are many hypotheses based on extrahepatic factors, for instance the enterohepatic circulation, as well as on hepatic factors.

The evaluation of the BSP metabolism may be done in two ways. According to the original method the *retention* of BSP in the blood is determined at a certain

interval, usually 45 min. after the administration of the substance (Rosenthal & White, 1925; see also Herlitz, 1927). In this way only one determination of the concentration of BSP in blood is needed. The amount of BSP injected must be exactly known. However, in this evaluation also the first and the third phases, which do not refer exclusively to the elimination of BSP from the blood, are included.

Another way is to calculate the *rate of elimination* of BSP from plasma, usually expressed in terms of half life of BSP. This is computed only from values received during the second phase.

Experimental

The performance of the bromsulphthalein test.—A 5 per cent solution of BSP was intravenously injected in an amount of 5 mg per kg body weight. The injection was given in a scalp vein in infants and on a cubital vein in children above infant age within the course of half a minute. The substance was given in the morning when the children were fasting. Blood samples were taken by finger puncture (capillary blood) at various intervals within 2-20 min. after the injection. Usually 4 blood samples were taken. Samples with hemolysis were discarded.

The values for BSP concentration in serum were plotted on a semilogarithmic paper against time in minutes. Inspection of the semilogarithmic plots demonstrated that in all patients in this investigation one exponential adequately described the fall in serum BSP during the interval studied. The half life of BSP in serum was then graphically calculated.

Determination of bromsulphthalein in serum.—The disadvantage of the original method was, at least in pediatric practice, that an amount of 1-2 ml blood was needed for the analysis. In 1954 Hoffman & Oettel described a micromodification of the method, according to which only 0.2 ml blood is

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TABLE 1. *Bromsulphthalein half life related to various laboratory findings in eight cases of hepatitis.*

Subject and sex	Age (years)	Icteric index (Meulengracht) 2-8 ^b	Thymol turbidity (ext.) <0.120 ^b	Alkaline phosphatases (units acc. to Bodantsky) 2-14 ^b	Citric acid (μ g/ml) 15-28 ^b	Bromsulphthalein half life (min.) See text
1. ♂	3/12	44	0.07	40	—	6.1
2. ♂	5/12	24	0.05	18	24	6.5
3. ♂	5	20	0.08	16	30	8.0
4. ♀	6	6	0.78	14	41	11.5
	—	5	0.57	14	—	7.4
	6 3/12 ^a	11	1.00	9	29	18.1
	—	7	0.90	12	96	10.1
	—	4	0.45	13	—	7.2
5. ♂	10	8	0.80	20	—	17.2
6. ♀	10	15	0.59	13	—	7.2
7. ♀	12	5	0.47	13	—	5.7
8. ♀	14	24	0.02	14	29	8.3

^a Case 4 was readmitted to the clinic at an age of 6 years and 3 months on account of a relapse.

^b Normal values.

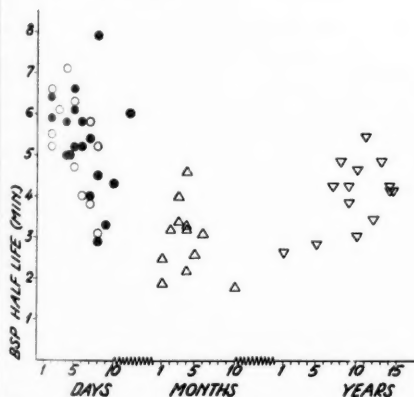


Fig. 1. Bromsulphthalein (BSP) half life in normal subjects of different ages and in newborns with so-called physiologic jaundice. ○, normal newborns; ●, icteric newborns; △, normal infants; ▽, normal children.

read against the blank in a Beckman B spectrophotometer at 575 $m\mu$ in semimicro-cuvettes. The concentration of bromsulphthalein is calculated from a standard curve.

The material of the investigation.—The material comprised 5 series. The first consisted of fourteen "normal" children in an age of 1-14 years, and the second of twelve "normal" infants in an age of 1-12 months. These children were under observation in the Clinic on account of social grounds, or some psychosomatic disorder, as enuresis, encopresis etc., or a localized disorder, as eczema, fracture, etc. Their general condition was good without any signs of liver affection. The third series consisted of twelve normal newborns without visible jaundice. The fourth series comprised eighteen newborns with jaundice in absence of hemolytic disease or significant incompatibility between mother and child according to the Rh and ABO systems, one third of which were premature (birth weight about 2000-2500 g) and two thirds of which were fullterm. All the children of this series had a marked jaundice, but were otherwise in a good condition. The fifth series consisted of eight cases of hepatitis, the diagnosis of which were formed before the BSP test was carried out.

necessary. The principle of the method is as follows: the blood sample (0.2 ml) is diluted with 0.9 ml of a citrate buffer (pH 6.5). After centrifugation 0.05 ml of a NaOH solution (1 per cent) is added to 0.4 ml of the supernatant. The same amount is also mixed with 0.05 ml of the citrate buffer (blank). The extinction of the solution is

Results

The results are presented in Fig. 1 and Table 1. In *Series I* (normal children, age 1-14 years) [Fig. 1] the half life of BSP was found to be 4.0 ± 0.22 min. (Mean \pm S.E.). This is in general agreement with the results obtained by Dost & Goetze (1956) who in a corresponding age group found a mean half life of 4.7 min. These values are within the same limits as those found in adults (Mateer *et al.*, 1943; Lavers *et al.*, 1949; Goodman, 1952). In *Series II* (normal infants outside the newborn period) [Fig. 1] a mean half life of 3.0 ± 0.24 min. was found. The difference between the means of Series I and II is statistically significant ($P < 0.01$). Dietel (1956) has earlier reported—without giving any direct data—that there is no marked difference in BSP half life between infants and older children. In *Series III* (normal newborns) [Fig. 1] a mean half life of 5.3 ± 0.35 min. was found. The difference between Series II and III is statistically significant ($P < 0.01$).

The results of the determinations in *Series IV* (icteric newborns) are presented in Fig. 1. As no correlation was seen between the BSP values and the body weight of the babies, the premature and fullterm infants were added to form one group. The mean half life of BSP in this series was found to be 5.3 ± 0.29 minutes. Thus no significant difference in BSP half life was found between the icteric and non-icteric newborns. The values for the bilirubin in serum in Series IV varied between 11.3 and 23.3 mg per 100 ml, with a mean of 17.4 ± 0.9 ; none of the determinations showing any direct reacting bilirubin.

As no difference was seen between the

newborns of Series III and IV they were added to form one group. It is seen that the BSP half life values are highest in the first days after birth and then rapidly decrease within the following days of the newborn period, reaching values comparable to those found in the rest of infancy. The regression coefficient calculated from these values ($b = -0.18$) is almost significant ($0.01 < P < 0.05$).

In eight children with hepatitis (*Series V*) the mean half life of BSP was found to be 7.8 min.; as seen from Table 1 the scattering of the values in this series was high. It is to be noted, however, that the infants of this group showed relatively low values.

Discussion

In the normal material of the present study, i.e. the subjects without signs of liver affection, the elimination rate of BSP varied significantly between the various age groups investigated. The lowest rate was found in the newborns. The increased half life values observed in the present investigation are in general agreement with high retention values reported by Herlitz (1927) and Yudkin *et al.* (1949). In general terms the low elimination rate of BSP may be explained as due to physiologic immaturity of the liver; to precise the closer nature of this is, however, difficult. Yudkin *et al.* (1949) has pointed out circulatory adjustments in the first few days after birth as a possible cause but other factors are probably also involved. It is, however, apparent that there is a very rapid improvement of the excretory liver function; as shown in the present study the elimination rate of BSP increases within 1-2 weeks after birth to values

normal for infants outside the newborn period.

The highest elimination rate of BSP was found in infants outside the newborn period. This high capacity of the liver to clear BSP from blood, may, at least partly, be explained by a greater size of the liver in relation to body weight in this age as compared to later in life (see Brock, 1954). Another factor acting in the same direction may be a relatively greater blood flow through the liver on account of a greater cardiac output per minute in relation to body-weight during the same period of life (see Smith, 1953; Brock, 1954).

In the present investigation no difference in the elimination rate of BSP was observed between the non-icteric newborns and the newborn with so-called physiologic jaundice. From this it may be concluded that probably no general damage of the liver cells is involved in the etiology of physiologic jaundice, nor a blocking of the bile flow to the intestine. If so, a lower elimination rate had to be expected in the newborns with this disorder as com-

pared to the non-icteric newborns. Furthermore, it may be said that, if at all, physiologic jaundice is caused by a decreased liver function, this must be limited to comprise only certain biochemical activities. Recently it has also been shown that the cause of the disturbance of the bilirubin metabolism may be a defect in the ability of the neonatal liver to perform glucuronide conjugation (Brown *et al.*, 1958); these authors found in the fetal and newborn guinea pig defects in two enzymatic steps in the glucuronide synthesizing system.

In all cases of hepatitis the elimination rate of BSP was decreased. As seen in Table I there was no statistically significant correlation between the BSP half life and the other laboratory findings.

It appears that measurement of the elimination rate of BSP is a method which is useful in pediatric practice; it is sensitive and gives consistent values, is also fairly simple to perform. It may especially be of value in diagnostics of hepatitis in absence of jaundice.

Summary

The elimination rate of bromsulphthalein (BSP) from plasma evaluated in terms of BSP half life has been studied in various patient groups. In normal subjects the values obtained varied significantly between different age categories. Highest values were found in newborns ($M = 5.3$ min.), the values then rapidly decreased to low values in infancy ($M = 3.0$ min.), and thereafter again increased to higher values during childhood ($M = 4.0$ min.).

In a series of hepatitis the BSP half life was consistently longer than in the normal subjects, indicating the technique used as an available method in assessing liver function in children.

No difference in the elimination rate of BSP was seen between non-icteric newborns and newborns with so-called physiologic jaundice. The etiology of physiologic jaundice has been discussed according to these results.

Recherches sur le taux d'élimination de la bromosulfaléine

Le taux d'élimination de la bromosulfaléine du plasma, exprimé par la durée du temps nécessaire pour que la concentration initiale tombe de cinquante pour cent, a été étudié sur différents groupes de patients. Chez les sujets normaux, les valeurs trouvées accusèrent des variations significatives pour les différentes catégories d'âge. Les taux les plus élevés furent trouvés chez les nouveau-nés ($M = 5,3$ min.); on observa ensuite une chute rapide de ces taux qui tombaient à des niveaux peu élevés chez les nourrissons ($M = 3,0$ min.) pour remonter à des niveaux plus élevés chez les enfants ($M = 4,0$ min.). Dans un groupe de malades affligés d'hépatites, les temps trouvés pour que la concentration tombe à cinquante pour cent de sa valeur initiale ont été chaque fois plus longs que chez les sujets normaux; il en résulte que la technique utilisée peut servir d'épreuve pour le contrôle de la fonction hépatique chez les enfants. Aucune différence dans le taux d'élimination de la bromosulfaléine n'a été constatée entre les nouveau-nés non icériques et les nouveau-nés atteints d'ictère dit physiologique. L'étiologie de l'ictère physiologique a été discutée à la lumière de ces résultats.

Studien über die Ausscheidungsgeschwindigkeit von Bromsulphthalein bei Säuglingen und Kindern

Die Ausscheidungsgeschwindigkeit von Bromsulphthalein (BSP) aus dem Plasma, ausgedrückt in BSP Halbleben, wurde bei verschiedenen Krankengruppen untersucht. Bei normalen Personen unterschieden sich die erhaltenen Werte in den verschiedenen Altersgruppen bedeutend. Die höchsten Werte wurden bei Neugeborenen ($M = 5,3$ Min.) gefunden; sie nahmen dann rasch ab und sanken bis zu $M = 3,0$ Min. bei Säuglingen, um wieder anzusteigen und $M = 4,0$ Min. im Kindesalter zu erreichen. Bei einer Krankenreihe mit Hepatitis war das BSP Halbleben beständig länger als bei normalen Individuen, ein Hinweis darauf, dass die angewandte Technik ein Verfahren zur Bestimmung der Leberfunktion darstellen könnte. Es wurde kein Unterschied in der Ausscheidungsgeschwindigkeit von BSP zwischen nicht-gelbsüchtigen Neugeborenen und solchen mit sogenanntem physiologischen Icterus festgestellt. Die Ätiologie des physiologischen Icterus wird auf Grund dieser Befunde erörtert.

Estudios sobre la tasa de eliminación de la Bromosulfaleína en lactantes y niños

La cuota de eliminación de la Bromosulfaleína (BSP) del plasma, valorada de acuerdo a la duración de su vida media, ha sido estudiada en diversos grupos de pacientes. En individuos normales los valores obtenidos varían significativamente con los diferentes grupos de edades. Los valores más altos de la serie fueron hallados en recién nacidos ($M = 5,3$ min.), decreciendo luego hacia valores más bajos en lactantes ($M = 3,0$ min.), y creciendo luego hacia valores más elevados en la niñez ($M = 4,0$ min.). En las series de hepatitis la vida media de BSP fué considerablemente más larga que en los casos normales, indicando que la técnica utilizada es un método válido en el estudio de la funcionalidad hepática en el niño. No se observaron diferencias entre las cuotas de eliminación de BSP de recién nacidos no ictericos y aquellos que presentaban la llamada Ictericia Fisiológica. La etiología de la Ictericia Fisiológica es discutida de acuerdo a estos resultados.

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University Pediatric Clinic
Barnsjukhuset
Göteborg
Sweden

A Comparison of the Electrolyte and Water Content of the Tissues in Experimental Nephrosis and Low Protein Diet in Rats

by H. ELLIS C. WILSON

The object of this investigation was to find out what relation there might be between rats with albuminuria on the one hand and those fed a low protein diet on the other. The two conditions present several known features in common: namely a loss of protein, in the one case by the kidney, in the other by deprivation; a fall in the plasma proteins and an increase in total body water. Both groups may show a clinical and a biochemical oedema. The mechanism of oedema formation in nephrosis has never been entirely explained and in general it is accepted that extra renal factors are concerned. Those considerations led one to see in what way the oedema of a low protein diet resembled that of nephrosis and to exploit if possible the low protein fed animal as a means of investigating this problem dissociated from any pathological lesion.

Dicker in a comprehensive series of papers showed that in rats on low protein diets although the total body water may increase by 1–2 per cent there is a marked shift of water from the cells to the extracellular space which may be increased 100 per cent. He also showed that there is a delay in the excretion of a standard

water load, which was due largely to an increase of an antidiuretic substance which could be extracted from the urine. In humans with malnutrition or low protein diets a similar increase in antidiuretic activity has been observed. Nephrosis also has been shown to be associated with an increased amount of an antidiuretic substance in the urine (Arneil & Wilson). This was identified as pitressin in the body fluid of nephrotics (Wilson & Muirhead). In human nephrosis there is also an increase in aldosterone secretion (Luetscher). This substance has not yet been shown to be increased in animals or humans on low protein diets. The cause of the increased amount of those two hormones in nephrosis has hitherto not been explained from what is known of the physiology of those two secretions and Verney has shown that an increase in the osmolar concentration of the blood is an effective stimulus to pitressin secretion. In nephrosis on the other hand the tendency is for the osmolar concentration to be low. In the case of aldosterone (Bartler *et al.*) it has been shown that a fall in the extracellular volume of the tissues is a stimulus to an increase of secretion. In nephrosis

on the other, hand the extracellular volume is increased. It should be noted, however, that the plasma volume does not share in this increase and is indeed often reduced during the oedematous stage (McArthur). The oedema of nephrosis might hence appear to be due to a considerable degree to the increase in those two hormones causing salt and water retention. The causal mechanism is however obscure whether directly due to the renal lesion or indirectly to the protein loss. The above consideration led one to examine the tissue electrolytes in experimental nephrosis in rats and in those on a low protein diet.

Methods

The experimental data were planned to obtain the total water Na, K and Cl content of muscle and liver on a fat-free dry weight basis. The blood total proteins Na, K and Cl were estimated and hence figures were obtained for calculating the distribution of water between the intracellular and extracellular spaces. Diuresis experiments were also carried out with known doses of Na and K salts in order to obtain indirect evidence of the activity of a salt retaining corticoid.

Rats of both sexes (segregated) and weighing between 200 and 250 g were put on a low protein diet of the following composition: 500 g carrots, 36 g starch, 60 g lard, 3.5 g salt mixture, plus 3% cod liver oil. The rats were sacrificed after 6-10 weeks on the diet.

Nephrosis rats

These were between 100 and 150 g weight and were fed the usual stock diet of the controls. Anti-rat kidney serum was prepared and administered according to the method employed by Heyman *et al.* The animals were sacrificed after having a steady albuminuria of at least 1-2 g per cent for over 4-8 weeks. Normal rats often excrete a small

quantity of protein but the protein in those experimental animals was extracted from the urine and found to be rat plasma albumen by means of paper electrophoresis.

Experimental Results

The results show that all experimental groups, namely the low protein, gelatin, and the albuminuric showed an increase in total water content and a decrease in

TABLE 1

	No. of animals	H ₂ O % wet weight	K per 100 g fat-free dry weight m.eq.	Na per 100 g fat-free dry weight m.eq.
Controls	31	75.1	50.4	9.3
Low protein	21	76.8	43.8	16.0
Controls	11	74.1	48.9	
Low protein	14	77.5	39.3	
Albuminuric	9	76.1	42.1	
Controls ^a	31	75.1	44.7 ^a	
Gelatin ^a	26	76.3	38.6 ^a	

^a Dry weight only.

Difference of average of H₂O of controls & low protein group = 1.7 ml

$t = 3.4; .01 > P > .001$

Difference of average of K of controls and low protein group = 6.4 m.eq.

$t = 3.6; .01 > P > .001$

Difference of average of Na of controls & low protein group = 6.7 m.eq.

$t = 3.5; .01 > P > .001$

Difference of average of H₂O of controls & low protein group = 2.4 ml

$t = 3.0; .01 > P > .001$

Difference of average of H₂O of control & albuminuric group = 1.4 ml

$t = 2.6; .05 > P > .02$

Difference of average of K of controls & low protein group = 9.6 m.eq.

$t = 3.5; .01 > P > .001$

Difference of average of K of controls & albuminuric group = 6.8 m.eq.

$t = 2.4; .05 > P > .02$

Difference of K of controls & gelatin group = 6.1

$t = 4.7; .001 > P > .0001$

TABLE 2

	No. of animals	Average extracellular vol. ml	Intracellular vol. ml	Na + K in cell m.eq.	Na + K per litre muscle water m.eq.
Controls	11	14.2	59.9	194.0	190
Low protein	14	26.9	50.6	191.5	157.0
Albuminuric	10	15.5	60.6	162.0	140.9

Difference of av. extracellular vol. of low protein & control group = 12.6 ml

$t = 5.6; .001 > P > .0001$

Difference of av. Na + K per litre muscle water of controls & low protein group = 39.8 m.eq.

$t = 3.2; .01 > P > .0001$

Difference of av. Na + K in cell of controls and albuminuric group = 32.0 m.eq.

$t = 4.06; .001 > P > .0001$

Difference of Na + K per litre of muscle water of controls & albuminuric group = 49.1 m.eq.

$t = 3.4; .001 > P > .0001$

potassium per unit of dry weight compared to the normal (Table 1). The differences are all significant. The potassium content fell between 12–19 per cent in the low protein group and 15 per cent in the albuminuric group. Further information can however be obtained from a calculation of the size of the tissue spaces and the concentration of electrolyte in the cell and total muscle water. In the low protein group, although the water content has increased only 1.5 to 2.0 (Table 2) there has been a marked shift in the distribution of water between the two spaces. The extracellular space has increased from 14.2 ml per 100 g wet weight to 26.5 ml associated with an almost equal decrease in cell volume. In the albuminuric group although the water content has increased there is no change in the distribution of water between the two spaces. Both those groups show a marked fall in K per g of

TABLE 3. *Per cent excretion in 4 hours.*

	H ₂ O	Na	Cl
Control 5% of body weight of 9% NaCl	36.4	34.4	32.8
Low protein, as above	38.4	42.4	33.9
Albuminuric, as above	36.5	27.2	38.2

	H ₂ O	K	Cl
Control 5% of body weight of 1.2% KCl	68.2	72.1	87.3
Low protein, as above	81.0	54.5	63.6
Albuminuric, as above	69.3	60.4	68.9

dry fat-free weight. This would have entailed a fall in concentration of the electrolytes Na and K in the cell had there not been a shrinkage in cell volume in the low protein group which compensates and brings the concentration up to that of the controls. The concentration of Na and K in the cells of the albuminuric group on the other hand is about 20 per cent below that of the controls.

A few diuresis experiments showed no circumstantial evidence of an increased activity of the salt retaining corticoid in the low protein group (Table 3). The excretions of NaCl and H₂O were almost identical with those of the control. The albuminuric group on the other hand showed a somewhat reduced excretion of Na but not of water or chloride. After a test load of KCl the low protein group excreted considerably more H₂O but less K and Cl than the controls. The relative retention of K and Cl was probably due to an uptake of K by the depleted cells and associated possibly with an extrusion of Na from the cells which would thus combine with the Cl fraction and remain in the extracellular phase. It should be noted that the KCl caused a greater output of water in the low protein group compared to the controls. Apparently the diuretic

effect of KCl overcomes the increased activity of the antidiuretic hormone which is shown up by a water diuresis.

The problem remains to try to equate the observations recorded here with the type of individual protein loss. The low protein group are subjected to a general protein deficit and all tissues make a sacrifice in certain proportions probably much as in starvation. The muscles and liver give up a considerable proportion of their protein in starvation. The suggestion is made that the shrinkage of the cell is a physiological response to protein loss and an attempt to keep the osmotic pressure normal within the cell. The loss of protein in the rats with albuminuria is both relative and selective, namely the plasma albumen. The protein intake was the same as in the control group and although there is an interchange (Smith *et al.*) of protein between tissue cells and plasma, the cells themselves are at least at one remove from the direct loss of protein, namely the plasma albumen in the urine. The primary response to a plasma albumen loss might hence be expected to be a fall in albumen—that is qualitative change in the plasma protein pattern and possibly a reduction in plasma volume. A reduction in plasma volume has been noted in human nephrotics during the oedematous stage (McArthur). It should also be noted (Table 4) that although the plasma proteins have fallen below normal in both the low protein and

TABLE 4

	Average total plasma protein g %	Average total plasma cholesterol mg %
Normal	7.2	67.0
Low protein diet	5.4	45.4
Albuminuric	5.2	155.0

albuminuric groups, the plasma cholesterol has fallen slightly in the former and increased considerably in the latter. It is evident from the facts obtained that the process of oedema formation in the two conditions are not identical in every respect at least at the stage at which the animals were sacrificed.

The following features appear to be common to both: (1) Fall in plasma albumen; (2) fall in potassium per unit of dry weight; (3) increase in H_2O in the tissues.

They differ on the other hand in the following respects: (1) Cell shrinkage in the low protein group which compensates for the loss of K and keeps the osmolar concentration normal; (2) the cells maintain their volume in the albuminuric group but are hypotonic; (3) there is no indirect evidence of the activity of a salt retaining corticoid in the low protein group; (4) the plasma cholesterol is increased in the nephrotic and decreased in the low protein group compared with the controls.

Summary

The metabolic effects of an overall protein loss by deprivation and a selective loss from a particular tissue are not entirely identical at the stage in the process at which the animals were sacrificed. It would appear that nephrosis is associated with some other metabolic disturbance than that caused by a mere loss of protein.

Comparaison de la teneur des tissus en électrolytes et en eau chez des rats atteints de néphrose expérimentale et chez des rats soumis à un régime pauvre en protéines.

Les effets métaboliques d'une carence protidique générale par privation et ceux de la carence sélective d'un tissu donné ne sont pas tout à fait identiques au stade du processus auquel les animaux ont été sacrifiés. Il semblerait que la néphrose s'accompagne d'autres troubles métaboliques que ceux qui résultent d'une simple carence en protéines.

Ein Vergleich zwischen dem Elektrolyt- und Wassergehalt der Gewebe bei experimenteller Nephrose und eiweissarmer Diät bei Ratten.

Der Stoffwechseleffekt von allgemeinem Eiweissverlust infolge von Eiweissunterernährung und selektivem Verlust in einem besonderen Gewebe ist in dem Stadium des Prozesses, wenn die Tiere getötet wurden, nicht vollkommen identisch. Es erscheint, dass Nephrose mit anderen Stoffwechselstörungen als den durch blossen Eiweissverlust bedingten, verbunden ist.

Estudio comparativo sobre el contenido en agua y electrolitos en los tejidos de ratas sometidas a dietas pobres en proteínas y en la nefrosis experimental.

Los efectos metabólicos de una pérdida global de proteínas por carencia, y de una pérdida selectiva a partir de un determinado tejido, no son completamente idénticas en la etapa del proceso en la cual los animales fueron sacrificados. Parece como si en la nefrosis se encontraran asociados otros tipos de trastornos metabólicos, a más de los provocados por la sola pérdida de proteínas.

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Biochemical Dept.
Royal Hospital for Sick Children
Yorkhill
Glasgow, C.3
Scotland

From the Children's Hospital, Fuglebakken, Copenhagen (Chief: A. Rothe-Meyer, M.D.), and the Roentgen Department, Copenhagen County Hospital, Gentofte (Chief: E. de Fine Licht, M.D.)

Radiography of Stomach in Hypertrophic Pyloric Stenosis

In Acute Phase and the First Few Months after Surgical or Spasmolytic Treatment¹

by O. STEINICKE and M. ROELSGAARD

Meuwissen & Sloff were the first to point out, in 1932, that hyperperistalsis, dilatation of the stomach, and retention are not sufficient evidences for the radiographic diagnosis of hypertrophic pyloric stenosis (pyl. sten.). To be certain of the X-ray diagnosis a 2–3 cm long constantly strictured pyloric canal must be demonstrated, too. This view has since been borne out by several writers, e.g. Wallgren (1937), Runström (1939), and Calvin & Denenholz (1941). Olmick & Weens (1949) regard the cord-like pyloric canal as pathognomonic of pyl. sten., and call attention to the fact that the narrowed area comprises not only the pylorus itself, but also the distal hypertrophic segment of the prepyloric portion. This latter point is very important, as it disproves the previous view of the disease as limited to the pyloric canal. Another characteristic radiographic feature, that of an impression in the duodenal bulb, has likewise been pointed out by a number of the above writers.

In spite of the demonstrations of these various characteristics, the X-ray diagnosis may occasionally be difficult in infants with pyl. sten., particularly owing to difficulties of obtaining distinct pictures of the prepyloric portion. Astley in 1952, and in 1956, published papers in which he gives a detailed description of the most appropriate technical procedure of radiography in infants with pyl. sten. He also states, that the time elapsing before the contrast medium begins to pass through the pylorus need not be prolonged. The stomach nevertheless as a rule empties more slowly than normally. Further, Astley shows that the narrowed prepyloric portion may vary somewhat in caliber in the individual cases, but he does not state exactly how great these variations are. Nor do we get an information about the frequency of such deviations from the previously accepted characteristic X-ray picture of pyl. sten. Whether the time of onset and the severity of the symptoms, as well as the interval between the onset

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TABLE 1. X-ray findings in surgically treated infants with pyl. sten., before and after operation.

No. A	Age in days		Preop. X-ray exam.						Early postop. X-ray ex.				Late postop. X-ray exam.							
	At onset of symps.	At operation	No. of days before operation	Dilat. of stomach	Delayed emptying	Varied lumen	Length of sten. in mm	Breadth of sten. in mm	No. of days after operation	Dilat. of stomach	Delayed emptying	Varied lumen	Length of sten. in mm	Breadth of sten. in mm	No. of months after operation	Dilat. of stomach	Delayed emptying	Varied lumen	Length of sten. in mm	Breadth of sten. in mm
32	18	23	2	+	+	-	20	1												
26	20	26	2	+	+	-	15	1												
24	18	29	2	-	+	+	15	4												
5	25	32	2	+	+	-	20	2												
35	21	33	1	-	-	-	15	1												
12	21	35	3	+	+	-	20	2												
19	21	37	4	+	+	+	15	3												
23	7	40	4	+	+	-	15	2												
34	28	40	2	+	+	-	20	2												
16	28	48	3	+	+	-	20	2												
14	30	55	4	+	+	+	20	4												
20	35	55	1	+	+	+	15	4												
27	28	59	1	+	+	-	15	2												
15	30	84	8	-	+	+	20	4												
33	21	27	1	-	+	-	25	2	12	-	-	+	20	7						
9	21	28	1	-	+	-	15	1	8	-	-	+	15	5	3	-	-	+	10	9
31	24	31	1	+	+	-	15	3	13	-	-	+	15	6						
30	14	33	2	+	+	-	20	2	8	-	-	+	15	7						
29	38	44	1	+	+	-	25	1	7	-	-	+	20	7	10½	-	-	+	8	13
13	40	47	2	+	+	-	20	1	11	-	-	+	20	6	5½	-	-	+	15	9
18	21	48	3	+	+	-	20	2	7	-	-	+	20	10						
25	28	49	1	+	+	-	15	1	8	-	-	+	15	10						
22	21	49	3	+	+	-	20	1	9	-	-	+	20	8						
11	14	34							10	-	-	+	15	6						
3	21	37													7	-	-	+	20	10
8	33	40													13	-	-	+	15	9
17	39	45													18	-	-	+	10	11
2	35	46													5½	-	-	+	10	8
6	42	52													7	-	-	+	10	10
1	21	60													3	-	-	+	13	6
4	49	69													7	-	-	+	17	12
															3	-	-	+	15	7

and the X-ray examination have any influence on the radiographic findings, are also questions that remain to be answered. Finally, the radiographic changes occurring within the first few weeks or months after surgical or commenced spas-

molytic treatment have not been definitely clarified either. The investigation here reported were carried out with a view to throwing further light on some of these problems.

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Fig. 1. (A.25.) Boy, aged 7 weeks, with pyl. sten. symptoms since the age of 4 weeks. X-rayed one day before operation. The picture, taken 20-30 m.p.e., shows cord-like narrowing of the distal 15 mm of the prepyloric portion. No emptying of the contrast medium beyond slight filling of the duodenal bulb, at the base of which a marked impression is seen.



Fig. 2. (A.24.) Girl, aged 4 weeks, with pyl. sten. symptoms since the age of just under 3 weeks. X-rayed 2 days before operation. The picture, taken 10-15 m.p.e., shows a stomach of normal size, with scarce emptying of contrast medium only, as well as narrowing of the distal 15 mm of the prepyloric portion. Caliber of the narrowed area here 4 mm.

Material

Thirty-five infants with pyl. sten. had a total of 53 X-ray examinations of the stomach performed. The series comprises 29 boys and 6 girls, all admitted to paediatric units (19 to the Copenhagen County Hospital, Gentofte, and 16 to the Children's Hospital Fuglebakken) within the period from October 1954 to December 1957. Out of 31 surgically treated infants, 14 were X-rayed solely before the operation, nine both before and after, and eight only after. The remaining four examined infants were treated with spasmolytics only. Of these, three were X-rayed both before and after the treatment, and one not till after concluded treatment.

The X-ray examinations were performed after not less than 4 hours' fasting, and following administration of barium sulphate. The pyloric portion was examined specially in the right lateral position, where it is most readily projected free of the body of the stomach, and where the stomach empties most rapidly.

Results

The results of X-ray examinations of the surgically treated infants are recorded in Table 1, grouped according to time of examination. The ages of the infants at the onset of symptoms are recorded as accurately as possible in the Table, together with the exact age at operation.

In studying the X-ray photos attention was focused on the following facts, as illustrated in Table 1: (1) whether the stomach was dilated; (2) whether emptying of the stomach was delayed, i.e. did not start till 15-20 minutes after administration of the contrast medium; (3) whether variations could be observed in the lumen of the narrowed prepyloric portion; (4) the length (in mm) of the narrowed prepyloric portion; (5) the largest breadth of the narrowed portion (in mm).

Table 1 shows that pre-operative X-ray examination revealed dilatation of the stomach in most cases. In four of the ca-



Fig. 3. (A.11.) Girl, aged just over 6 weeks, with pyl. sten. symptoms since the age of 2 weeks. X-rayed 10 days after operation. The picture, taken immediately after administration of contrast medium, shows rapid emptying of the medium into the duodenal bulb. There is marked narrowing of the prepyloric portion with an abrupt transition to the proximal part of the antrum. Caliber of the narrowed area at least 6 mm.



Fig. 4. (A.29.) Boy, aged 12 months, with pyl. sten. symptoms since the age of 5 weeks. X-rayed 10½ months after operation. The picture, taken few m.p.e., shows rapid and normal emptying of the stomach. The prepyloric portion is not actually narrowed, but the filling is somewhat cone-shaped distally. The duodenal bulb normal.

ses under review such dilatation was not demonstrable, this being, accordingly, not a prerequisite of the X-ray diagnosis of hypertrophic pyl. sten.

The rapid emptying of the stomach characteristic of infants placed in the right lateral position is rarely seen in patients with pyl. sten. Our Case A.35 represents such an exception, rapid emptying of fairly large amounts of contrast medium having been demonstrated here. A normal or intensified peristalsis of the body of the stomach was seen in all cases, increasing towards the antrum, where strong contractions were demonstrated along both curvatures at the point of transition to the narrowed portion. This narrowed area usually covered the distal 15 to 20 mm of the prepyloric portion, and proper peristalsis was not detectable in this area. The caliber of the narrowed segment was in most cases constant (1–3 mm) (Fig. 1). In no more than four of the examined infants

(A.24, A.14, A.20, and A.15) did the caliber seem to vary somewhat, but it never exceeded 4 mm (Fig. 2). Furthermore, in the cases where tolerable filling of the duodenal bulb was obtained, a marked impression at the base of this was shown (Fig. 1).

X-ray examination of the stomach at varying intervals after pylorotomy showed the body to be normal in size. Emptying of the stomach was normal, large amounts of contrast medium were passing out very soon after the administration. But the prepyloric portion was still found to be narrowed, with an abrupt transition to the above-lying part of the antrum. However, in all the patients operated on a certain variation in the caliber of the narrowed portion was seen postoperatively, but without occurrence of proper peristalsis. The largest caliber of the prepyloric portion was considerably increased, even 1 or 2 weeks after the operation, ranging between 5 and 10 mm in the examined

TABLE 2. X-ray findings in spasmolytically treated infants with pyl. sten., before and after treatment.

No. A	Age in days		X-ray exam. before treatm.					Kind of treatment and duration in days	Days from start of treatment to radiography	X-ray exam. after started treatm.				
	At onset of symptoms.	On X-ray exam. before treatm.	Dilat. of stomach	Delayed emptying	Varied lumen	Length of sten. in mm	Breadth of sten. in mm			Dilat. of stomach	Delayed emptying	Varied lumen	Length of sten. in mm	Breadth of sten. in mm
10	14	32	+	+	-	15	2	Eumydrine: 18	20	-	-	+	15	6
28	22	26	+	+	-	15	1	Eumydrine: 22	4 23	-	-	-	12	2
21	56	77	+	+	+	25	4	Scopyl: 7 Pause: 10 Scopyl: 31	48	-	-	+	15	9
7	70							Eumydrine: 28 Pause: 14 Eumydrine: 42	28 89	+	+	-	15	1
										-	-	+	15	6

cases. The length of the narrowed area, on the other hand, seemed to be approximately the same during this period (Fig. 3)

Examinations carried out 3 to 10½ months after the operation showed the caliber to have increased further and the affected area to be shorter. Contractions were seen in all cases, especially along the lesser curvature. In five cases the degree of filling of the prepyloric portion was approximately normal, though with a cone-shaped tapering left distally, as for instance in patient A.29 (Fig. 4). Similar pictures were found in A.17, A.2, and A.1. In patient A.8, who 3 months after the operation presented a slight, but distinct narrowing, examination 5 months later revealed almost normal conditions, apart from a constant contraction 10 mm from the pylorus.

It should be mentioned that five of the infants operated on had been treated with

spasmolytics (scopyl or eumydrine) prior to operation and to the first X-ray examination. In three of these cases the treatment had been of less than one week's duration, while two had been treated for 2 or 3 weeks. As this treatment had had no clinical effect, and the results of examination did not differ from those of the other surgically treated infants in the acute phase, the stated five patients (A.19, A.15, A.31, A.27, and A.22) were included in the surgical group.

On the other hand, in the four infants submitted solely to medical treatment a marked clinical improvement was demonstrable. In two the attacks of projectile vomiting ceased shortly after the commencement of treatment. The two others relapsed, so that treatment had to be resumed. The results of X-ray examination are shown in Table 2, from which it appears that three infants were X-rayed

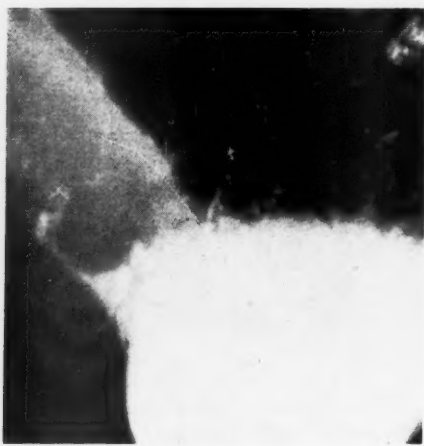


Fig. 5a. (A.7.) Girl, aged just over 3 months, with pyl. sten. symptoms since the age of just over 2 months. X-rayed after 4 weeks of eumydrine treatment. The picture shows a somewhat dilated stomach, and, apart from a small spot of contrast medium in the duodenal bulb, no emptying is seen. The distal 15 mm of the prepyloric portion present cord-like narrowing.



Fig. 5b. (A.7.) Same patient as Fig. 5a. X-rayed 2 months later after another 6 weeks of eumydrine treatment. The picture shows normal rapid emptying of the contrast medium. An abrupt transition is seen from the body of the stomach to the distal 15 mm of the prepyloric portion, which is seen to be narrowed, though with a caliber of up to 6 mm. A marked impression is found in the duodenal bulb.

both before and after the spasmolytic treatment, whereas one was examined only after commenced treatment. Excellent response was seen in the first three cases of the Table, the stomach emptying normally after 3 to 5 weeks of treatment, in patient A.28 even after 4 days. The filling of the narrowed prepyloric portion was also much better than before the treatment, in Case A.28, however, not on examination 4 days after commenced treatment, but plainly visible after 3 weeks. The last case stated in the Table (A.7) was X-rayed solely after commenced treatment. After 4 weeks of eumydrine therapy radiography revealed changes corresponding to those in the acute phase (Fig. 5a). After another few weeks of eumydrine administration normal conditions of emptying were seen, as well as a

distinctly varied filling of the prepyloric portion (Fig. 5b).

Discussion and Conclusion

In hypertrophic pyl. sten. the diagnostic aid of radiography of the stomach is open to discussion. In the great majority of cases the diagnosis can be made on the basis of the clinical findings alone. There will, however, always be cases in which the diagnosis is not quite evident, especially where no pyloric tumour is palpable. Though Craig (1955) holds that a palpable pyloric tumour is not invariably a sign of pyl. sten. during the first 14 days after birth, this symptom must nevertheless be regarded as an essential factor in support of the diagnosis and thus make X-ray examination unnecessary. The differential diagnosis of pyl. sten. from such diseases

as hiatus hernia, intestinal malrotation, duodenal atresia, pylorospasms, and cerebral vomiting is often difficult. In such cases radiography of the stomach with a procedure recommended by Astley can practically always confirm or refute a diagnosis of hypertrophic pyloric stenosis.

A knowledge of the radiographically demonstrable changes in the stomach seen in pyl. sten. is therefore useful, and not the least of the variations of these. It should be emphasized that although dilatation and delayed emptying of the stomach are the rule, one or both of these phenomena may be absent. In one out of 26 examined cases of our series there was found rapid and apparently normal emptying of the stomach. This experience suggests that the X-ray diagnosis should be based mainly on the presence of a constantly narrowed prepyloric portion displaying no peristalsis. Though our examinations showed that the lumen of the narrowed portion may vary somewhat in a few cases, the variations are relatively small, 4 mm being the largest caliber found. Even in such cases one is in no doubt about the presence of a marked narrowing, which at the same time is characterized by the absence of peristalsis. We have tried to make out, on the basis of the series under review, whether any difference could be detected clinically between the cases with radiographically demonstrable variations in the lumen of the prepyloric portion and the remaining cases with a uniformly strictured canal. For this purpose we included only patients X-rayed before any form of treatment had been given. The five infants in the surgical group given spasmolytic treatment prior to the examination were thus

ruled out. The series thereafter comprised 21 infants (18 from the surgical and three from the medical group). Of these, only four presented variations in the lumen of the prepyloric portion. Comparison of these four infants with the remaining 17 showed that the average age at onset of symptoms was 35 days for the four with variations of the prepyloric lumen against 23 days for the remainder. The age at onset of symptoms could, however, in few cases only be stated exactly, whereas the age at X-ray examination could be recorded with great accuracy. The average ages at radiography were 52 and 34 days respectively for the stated groups. The patients displaying some variation in the lumen of the narrowed area were chiefly infants whose symptoms had developed fairly late, and whose stomachs had not been X-rayed till after a relatively long interval. This might suggest that the infants were on their way to spontaneous recovery at the time of examination. More likely, however, the disease was of a milder character from the outset in these cases, with delayed manifestation of symptoms, and consequently later admission to hospital for further examination. The case reports available do not allow us to evaluate the severity of the cases in order thus to judge of the correctness of the above theory. Nor does the size of the tumour found at operation allow of conclusions in this respect.

A more certain evaluation of the severity proved to be possible through the radiographically demonstrated changes following surgical as well as medical treatment of pyl. sten. As stated under the results of radiography, the postoperative course was characterized by a normal rate

of emptying of the stomach already shortly after the operation. In addition, a gradually improved filling of the prepyloric portion was demonstrated, so that the radiographic findings could be regarded as approximately normal in most cases 6 or 7 months after the operation.

A similar improved emptying and increased lumen of the prepyloric portion was found in the four infants X-rayed following spasmolytic treatment. However, the examinations of these four infants as well as of the infants from the surgical group submitted to preparatory spasmolytic treatment showed that some time may elapse before the treatment effects radiographically demonstrable improvement. It is probably mainly due to the fact that oral therapy to infants subject to vomiting has little effect, unless the vomiting ceases immediately. This is in accordance with the observation that in

our series the cases displaying a poor clinical effect continued to show the same radiographic changes as untreated infants. Though the number of medically treated infants examined was small, these experiences tend to suggest that improved motility of the prepyloric portion is obtained more quickly and with greater certainty after surgical than after spasmolytic treatment. The fact that a rapid improvement of the motility of the affected portion of the stomach reduces the risk of permanent disturbances of motility (Steinicke Nielsen & Roelsgaard, 1956) argues in favour of surgical treatment of pyl. sten.

A further investigation into this question will be reported in a future work, which shows the X-ray findings through childhood in surgically as well as spasmolytically treated children with previous pyl. sten.

Summary

Thirty-five infants with hypertrophic pyl. sten. were submitted to 53 X-ray examinations of the stomach, some having been X-rayed before treatment, some both before and after, and some only after. Thirty-one of the infants were treated surgically and the remaining four with spasmolytics. The results have been assessed in relation to the time of examination, whether before, shortly after (from 7 to 13 days), or longer after (from 3 to 10½ months) the treatment. Though dilatation and delayed emptying of the stomach were the rule on radiography prior to the treatment, these phenomena were not invariably present, in contrast to a narrowed prepyloric portion with no peristalsis, which was found in all cases. The lumen of this area varied in few instances only, and the largest caliber measured was 4 mm. The infants displaying such variations of the lumen all seemed to belong to the least severe cases. Radiography after a short as well as after a longer interval from pylorotomy showed the stomach to be normal in size and the emptying to occur normally. In addition, a marked variation of a considerably increased prepyloric lumen was seen. In a few instances, X-rayed some months after the operation, the filling of the prepyloric portion had become approximately normal. Similar observations were made among the infants treated with spasmolytics, though in some of these a longer time elapsed before improvement was demonstrable radiographically. The

investigation gave the result that improved motility of the prepyloric portion is obtained more quickly and with greater certainty after surgical than after spasmolytic treatment. The fact that this no doubt reduces the risk of permanent disorders of motility calls for surgical treatment of hypertrophic pyl. sten.

Examen radiographique de l'estomac au cours de la phase aiguë d'une sténose hypertrophique du pylore et au cours des premiers mois qui suivent le traitement chirurgical ou spasmolytique

Trente-cinq nourrissons atteints de sténose hypertrophique du pylore ont fait l'objet de 53 examens radiographiques de l'estomac, certains d'entre eux ayant été radiographiés avant le traitement, d'autres avant et après le traitement et certains uniquement après le traitement. Trente-et-un de ces bébés ont fait l'objet d'un traitement chirurgical et les quatre derniers ont été soignés à l'aide de spasmolytiques. Tous présentaient un rétrécissement de la portion prépylorique qui n'était le siège d'aucun mouvement péristaltique. La lumière de cette portion n'était variable que dans quatre cas et le plus grand diamètre que l'on ait pu mesurer fut de 4 mm. Les nourrissons chez lesquels ces variations de la lumière de la portion prépylorique furent constatées appartenaient, à ce qu'il semble, aux types les moins sévères. Les radiographies prises peu de temps après ainsi qu'au bout d'un long intervalle après la pylorotomie, montrèrent un estomac de dimensions normales dont la vidange s'opérait normalement. De plus, on observait des variations marquées de la lumière de la portion prépylorique dont le diamètre avait considérablement augmenté. Dans quelques cas, pour lesquels des radiographies furent effectuées au bout de plusieurs mois après l'opération, le remplissage de la portion prépylorique était à peu près normal. Des observations analogues ont été faites chez les bébés traités à l'aide de spasmolytiques, mais pour certains de ceux-ci, il fallut attendre plus longtemps avant qu'une amélioration pût être mise radiologiquement en évidence.

Röntgenologie des Magens bei hypertrophischer Pylorusstenose, in deren akuter Phase und den ersten Monaten nach operativer oder spasmolytischer Behandlung.

Fünfunddreissig Säuglinge mit hypertrophischer Pylorusstenose wurden im ganzen 53mal einer röntgenologischen Untersuchung des Magens unterzogen, manche vor der Behandlung, andere vor und nach und wieder andere nur nach der Behandlung. Einunddreissig unter ihnen wurden chirurgisch behandelt und die restlichen 4 mit Spasmolyticis. Bei allen Fällen fand sich eine enge präpylorische Portion ohne Peristaltik vor. Das Lumen dieses Abschnittes schwankte in seiner Weite nur bei wenigen Kindern und das grösste vorgefundene Kaliber war 4 mm. Die Kinder, die Schwankungen im Lumen aufwiesen, schienen zu dem weniger schweren Typus zu gehören. Die röntgenologische Untersuchung, die kurz nach der Pylorotomie oder viel später ausgeführt wurde, zeigte einen normal grossen Magen mit normaler Entleerung. Überdies konnte man bemerkenswerte Schwankungen in der Weite des beträchtlich vergrösserten präpylorischen Lumens beobachten. In einigen Fällen, die einige Monate nach der Operation röntgenologisch untersucht wurden, war die Füllung der präpylorischen Portion ungefähr normal. Ähnliche Beobachtungen wurden bei den mit spasmolytischen Mitteln behandelten Säuglingen gemacht, wenn auch bei einigen unter ihnen eine längere Zeitspanne vorüberging, bevor die Besserung radiologisch nachgewiesen werden konnte.

La radiografía de estómago en la estenosis pilórica hipertrófica, en la fase aguda y durante los primeros meses luego del tratamiento quirúrgico o espasmolítico

Treinta y cinco lactantes con estenosis pilórica hipertrófica fueron sometidos a 53 exámenes radiológicos de estómago, algunos fueron examinados antes del tratamiento, otros antes y después, y por último, otros lo fueron sólo después. Treinta y uno de estos lactantes fueron tratados quirúrgicamente y los restantes con espasmolíticos. En todos los casos fué hallada una región prepilórica estrechada y sin peristaltismo. La luz de esta zona varió en muy pocos casos, y el mayor calibre determinado fué de 4 mm. Los pacientes que exhibían variaciones en el diámetro de dicha región parecieron pertenecer a los tipos menos severos. Las radiografías efectuadas luego de cortos, así como de largos intervalos, después de la pilorotomía mostraron un estómago de lleno y dimensiones normales. Además, fué observada una marcada variación en la considerablemente ensanchada zona prepilórica. En unos pocos

casos, radiografiados algunos meses después de la operación, el lleno de ésta porción prepilórica fué aproximadamente normal. Entre los niños tratados con antiespasmódicos fueron efectuadas observaciones similares, aunque en algunos de ellos pasó un tiempo más largo antes de que se pudiera demostrar una mejoría radiológica.

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From the Municipal Out-patient Clinic for Allergic Diseases in Children, Copenhagen, Denmark (Physician-in-chief: E. Winge Flensborg, M.D.)

Continued Follow-Up Investigation Concerning the Fate of 298 Asthmatic Children

by ERIK RYSSING

The object of the investigation to be reported has been to study the spontaneous course of childhood asthma after the age of puberty.

In 1944 Flensborg (1) followed up a series of 298 asthmatic children who 5 to 18 years previously had been admitted to two pediatric departments in Copenhagen. None of the children had by that time received any desensitization treatment.

In 1957, i.e. 18 to 31 years after the stay in hospital, questionnaires were sent to the survivors. Information could be obtained concerning 281 out of the 283 survivors. The last two had emigrated to the U.S.A. with their family years ago.

Results

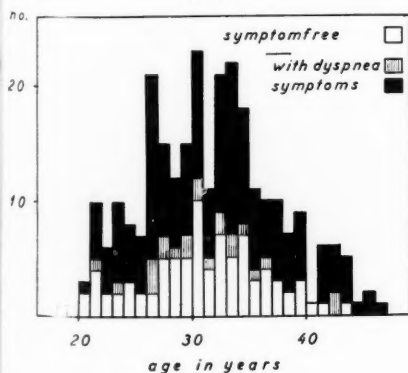


Fig. 1. The distribution according to age of the survivors in 1957.

Fig. 1 shows the age distribution of survivors in 1957. The patients were now all over 18 years of age, against a mere 131 in 1944. The symptom-free cases were equally distributed over all age groups.

Table 1 shows the states of the patients in 1944 and in 1957.

TABLE 1. States of patients in 1944 and 1957.

The number of patients without symptoms have decreased by years. As mentioned in the text the group of attack-free in 1944 and the groups of symptom-free in 1957 did not comprise altogether the same patients. The number of deaths have increased and about 55 % of the whole series are still suffering from asthmatic symptoms.

	1944		1957	
	No.	%	No.	%
Deaths from				
asthma	5	1.7	10	3.4
other causes	10	3.3	14	4.7
Attacks of asthma	163	54.7	—	—
Asthmatic symptoms	—	—	165	55.3
No asthma				
with dyspnea	53	17.8	22	7.4
without dyspnea	67	22.5	84	28.2
Unknown	0		3	1.0
Total	298		298	

In 1944, 5 patients had died but in 1957 a total of 9 patients had died from asthma at the age of $\frac{3}{4}$, 5, 14, 18, 18, 20,

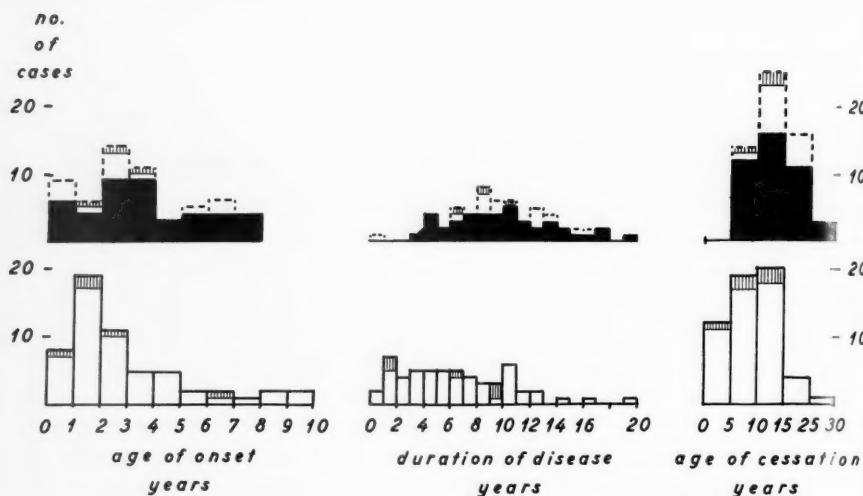


Fig. 2. A more detailed review of the states in 1957 of the 120 patients with no asthma in 1944. Blank columns are the patients with no symptoms in 1957 and the hatched columns the few who tend to shortness of breath. Black columns are the patients who were free from attacks in 1944 but now have experienced symptoms again. Blank columns with broken outlines are the patients who were free from attacks in 1944 but have experienced symptoms again and have been symptom-free for more than one year in 1957. The hatched columns with broken outlines are the few of these patients who tend to shortness of breath. Duration of disease is the time between onset and freedom from attacks before 1944. Age of cessation refers to informations obtained at the follow-up in 1944.

25, 25, and 27 years respectively and one from chronic bronchitis 30 years old.

One hundred and sixty-three had acute attacks of asthma in 1944, and 165 still had asthmatic symptoms in 1957, i.e. dyspnea and/or wheezing in association with change of weather, colds, bodily and mental strains etc. Twenty-nine had both acute attacks and symptoms.

In 1944, 120 had been free from attacks for more than one year, but they were not "cured". Thus, 53 were still suffering from shortness of breath, 8 from coughs, and 5 from expectorations. Emphysema or chronic bronchitis was probably present already then in a number of these cases.

In 1957, 106 patients had been symptom-free for more than 1 year though 22 of these tended to shortness of breath. A

closer analysis of these two latter groups showed that they did not comprise altogether the same patients.

States in 1957 of the 120 patients with no attacks in 1944

Table 2 shows that only 58 have remained free from symptoms since 1944.

TABLE 2. *States in 1957 of the 120 patients with no attacks in 1944.*

Free from symptoms since 1944	
without dyspnea	32
with dyspnea	6
Symptoms after 1944 but now symptom-free	
without dyspnea	13
with dyspnea	3
Symptoms in 1957	43
Deaths (1 from asthma)	2
Unknown	1
Total	120

Fifty-nine have experienced symptoms again and 43 still have symptoms in 1957. One has died from asthma. None of the 58 who have been symptom-free since 1944 have received desensitization treatment and only 3 of the 16 have received desensitization treatment. In other words, 71 have become symptom-free without specific desensitization treatment.

A more detailed review of the 120 cases appears to show that those children in whom the disease commences early, is of short duration and disappears before the age of 15 years have the greatest chance of becoming permanently symptom-free.

Thus Fig. 2 shows that of the 90 children who had become symptom-free before the age of fifteen, 51 (56.7%) have remained symptom-free since that time. As for the 24 children who had become symptom-free after the age of fifteen only 5 (21%) have remained free from symptoms.

Among the symptom-free in 1957 are 9 patients who tend to shortness of breath so that they probably have chronic pulmonary changes.

The 106 patients with no symptoms in 1957

As for the group of 106 with no symptoms in 1957, this comprises the 74 who had been symptom-free since 1944 plus 32 who had later become symptom-free.

Figure 3 shows the age distribution at cessation of symptoms. The hatched columns comprise the 22 symptom-free, though with a tendency to shortness of breath. The peak for cessation of symptoms lies within the years of puberty 10-15 years, with the majority outside this age-class, however.

Table 3 shows that 91 or 85 per cent

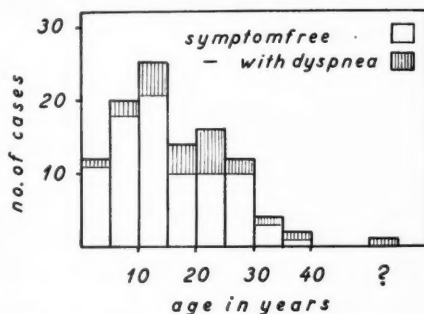


Fig. 3. The age distribution at cessation of symptoms.

TABLE 3. *Duration of freedom from symptoms before 1957.*

Years	Number
1-5	15
6-10	16
11-15	20
16-20	25
21-25	20
26-31	9
Unknown	1
Total	106

had been symptom-free for 5 years or more in 1957.

As none of the patients followed up in 1944 had received any desensitization treatment, this investigation could give information on the course of the disease during the observation period without specific treatment. Since then several patients have been treated, but of the 106 symptom-free in 1957 only 16 had received specific treatment, i.e. 90 patients or 30 per cent of the whole series of 298 had become symptom-free without desensitization.

In other words, only 30 per cent have grown out of the disease or become symptom-free following various forms of non-specific treatment.

The working capacity

Finally, the questionnaires also contained some questions to elucidate the working capacities of the 165 affected.

To the question: Can you manage full working hours? 135 answered yes, 16 answered no and 13 yes, but (1) with symptoms, (2) at a reduced pace, (3) with difficulty, and (4) with some days lost through sickness. Eleven patients now receive and 8 have received invalid pensions while 2 receive financial assistance for chronic illness.

Thus, a fairly large proportion managed full working hours. This was due partly to the fact that some had taken consideration of their disease when choosing occupation, and partly to the fact that several patients have only mild symptoms or rare attacks.

Discussion and Conclusion

Only a few studies on the spontaneous course of childhood asthma have been published previously.

About the half of Hamburger's (2) asthmatic children had become symptom-

free at the age of puberty. Tüscher (5) found freedom from symptoms in 54 % of 136 asthmatic children. Thirty-five children had become symptom-free before the age of puberty and 39 after the age of puberty. Mai (3) reported that 30 % out of 80 asthmatic children were relieved at the age of puberty. Rackemann & Edwards (4) reported a follow-up study of 688 patients after an interval of 20 years. Of the 449 children seen before 13 years about 30 % were "cured". Among Rackemann & Edwards' patients an unknown number of children have been given a not specified or brief course of specific treatment, so that the 30 % must be regarded as a maximum value.

We may conclude that childhood asthma tends but little to spontaneous cure, since no more than about 30 per cent become symptom-free after the age of puberty without specific treatment.

For this reason early diagnosis, careful allergologic examination and proper treatment during continued observation is very important in every case of asthma arising in infancy or childhood.

Summary

In a continued follow-up investigation, the status concerning 298 asthmatic children questioned in 1944 is reviewed. Information could be obtained concerning 281 out of 283 survivors.

Out of the 120 cases who were free from attacks in 1944 only 58 have since remained free from symptoms, 59 have experienced symptoms again and 43 still have symptoms. Out of the 59, 3 patients are now symptom-free, received desensitizing therapy. A more detailed review of the 120 cases appears to show that those children in whom the disease commences early, is of short duration and disappears before the age of 15 years have the greatest chance of becoming permanently symptom-free.

Only 106 (35.5 per cent) out of the 298 are now free from symptoms and only 16 out of the symptom-free patients have received desensitizing therapy, viz., only 90 patients or approximately 30 per cent have "grown out of" the disease or become symptom-free following various forms of non-specific treatment.

One hundred and sixty-five patients had symptoms in 1957, but 135 of them can carry out full-time work, 13 with difficulty and 16 not at all. Eleven patients now receive and 8 have received invalid pensions while 2 receive financial assistance for chronic illness. A total of 9 patients have died from asthma and one from chronic bronchitis.

Résultats d'un contrôle à long terme du destin de 298 enfants asthmatiques

L'auteur passe en revue l'état actuel de 298 patients asthmatiques qui avaient été hospitalisés dans leur enfance 18 à 31 ans auparavant. Des renseignements ont pu être obtenus pour 281 survivants sur 283. Sur les 120 enfants qui avaient cessé d'avoir des crises en 1944, 58 seulement en sont restés exempts depuis lors. Les enfants chez lesquels la maladie se manifeste de façon précoce, est de courte durée et disparaît avant l'âge de quinze ans ont les plus grandes chances d'en être délivrés définitivement. Sur l'ensemble des 298 patients de ce groupe, il n'y en a aujourd'hui que 106 (35,5 %) qui sont totalement exempts de crises et parmi ceux-ci il n'y en a que 15 qui ont été traités par une cure de désensibilisation. Par conséquent, il n'y a que 90 malades — soit environ 30 % — qui ont triomphé de leur maladie ou qui en ont été délivrés par l'une ou l'autre forme de traitement non spécifique. Cent soixante-cinq patients présentaient encore des troubles asthmatiques en 1957, mais 135 d'entre eux sont en mesure d'accomplir un travail à temps plein; 13 autres éprouvent des difficultés dans l'accomplissement de leur travail et 16 sont absolument incapables d'accomplir un travail quelconque. Onze de ces malades reçoivent actuellement une pension et 8 autres en ont reçu précédemment; d'autre part, 2 patients reçoivent une aide financière comme malades chroniques. Neuf patients sont morts d'asthme et un de bronchite chronique.

Fortgesetzte Nachuntersuchung über das Schicksal von 298 asthmakranken Kindern

Der gegenwärtige Zustand von 298 Personen, die als asthmakranke Kinder vor 18–31 Jahren im Krankenhaus behandelt worden waren, wird einer Untersuchung unterzogen. Auskünfte konnten über 281 von 283 überlebenden Individuen eingezogen werden. Unter 120 Kindern, welche im Jahre 1944 frei von Anfällen waren, sind nur 58 seither symptomfrei verblieben. Kinder, bei denen die Krankheit frühzeitig einsetzt, von kurzer Dauer ist und vor dem Alter von 15 Jahren verschwindet, haben die beste Aussicht, symptomfrei zu verbleiben. Von der Gesamtzahl von 298 sind nur 106 (d. i. 35,5 %) gegenwärtig symptomfrei, und nur 16 unter ihnen haben eine Hyposensibilisierungsbehandlung durchgemacht. Mithin sind nur 90 unter den Kranken oder 30 % der Krankheit „entwachsen“ oder mit Hilfe von verschiedenen nicht spezifischen Behandlungsmethoden anfallfrei gemacht worden. Einhundertundfünfundsechzig Kranke hatten noch Symptome in 1957, aber 135 unter ihnen können einer vollzeitigen Beschäftigung nachgehen, 13 nur schwierig und 16 gar nicht. Elf erhalten gegenwärtig und 8 erhielten früher eine Invalidenrente, während 2 finanzielle Unterstützung als chronisch Kranke erhalten. Neun Kranke sind an Asthma und einer an chronischer Bronchitis gestorben.

Estudio sobre la evolución y destino de 298 pacientes asmáticos seguidos desde su niñez

Se revée el estado actual de 298 pacientes asmáticos, hospitalizados cuando niños, entre 18 y 31 años antes. Se ha podido obtener información sobre 281 de 283 sobrevivientes. De los 120 niños que habían estado libres de accesos en 1944, sólo 58 han continuado sin síntomas desde entonces. En aquellos niños en que la enfermedad es de comienzo precoz, si ésta es de corta duración y desaparece antes de los 15 años de edad, se tendrán las mejores posibilidades de continuar permanentemente libre de síntomas. De el total de 298 sólo 106 (35,5 %) están al presente libres de síntomas y sólo 16 de entre ellos han recibido terapéutica desensibilizante. Por lo tanto sólo 90 de los pacientes, aproximadamente el 30 % “han salido con la edad” de la enfermedad, o evolucionado libres de síntomas, sometidos a tratamientos no específicos de diversos tipos. Ciento sesenta y cinco enfermos todavía presentaban síntomas en 1957, pero de ellos, 135 hacen sus tareas sin inconvenientes, 13 con dificultad y 16 están completamente imposibilitados. Ocho pacientes han recibido, y 11 todavía reciben pensiones en su condición de inválidos, mientras que otros 2 reciben asistencia económica por enfermedad crónica. Nueve pacientes han fallecido de asma y uno de bronquitis crónica.

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Virum
Denmark

A Correlation between Suckling Pressures and the Movements of the Tongue

by G. M. ARDRAN and F. H. KEMP

Cineradiographic studies of bottle feeding babies, lambs and kid goats (5) have shown that a filled teat is indented by the tongue. If the wall of the teat is soft the neck is occluded and the contents of the bulb are displaced into the back of the mouth. As the forepart of the tongue is raised the back of the tongue is lowered; thus suction is produced to aid the flow of milk from the teat into the mouth. When the bulb of the teat is empty, and the lower jaw and the forepart of the tongue are lowered, milk fills the teat and some passes through into the back of the mouth; the tongue movements being similar to those of a man sucking fluid through a straw (4).

This paper describes the results of simultaneous cineradiographic examinations with measurements of the pressure in the teat and mouth during feeding.

Method

Two lambs were fed from a bottle containing a suspension of 25% barium sulphate in calf feed (Levers "Lobol"), through a soft veterinary teat. Cineradiographs of the region of the mouth and upper pharynx were taken in the lateral projection at 50 frames per second. Pressures were recorded

with transducers of the Shillingford-Muller pattern. The transducer was connected to a water-filled polythene tube, 1 mm diameter at its open end. The frequency response of the system was 10 cycles per second. The position of the end of the tube in relation to the teat was varied; in different experiments the end of the tube projected into the mouth about 1 cm beyond the end of teat, or was fixed to the internal or external surface of the teat, either near the tip, in the centre of the bulb or in the neck. In some instances pressures were recorded from two sites at the same time. The exposure of each cineradiographic frame was recorded simultaneously. Fifteen babies were examined by these methods; a variety of different teats was used.

Seventeen babies suckling at the mothers' breast were also examined: a single fine polythene tube (0.5 mm internal diameter) with a small piece of tin foil at its tip was fixed to the mother's nipple with plastic skin; as the tin foil was radio-opaque the position of the end of the tube in the baby's mouth during suckling could be ascertained from the cineradiographs. When examining babies the cineradiographic exposure was limited to a maximum of 4 secs (0.3 r). Many pressure records were also taken at intervals during feeding without cineradiography.

When the recording tube was inside the rubber teat the base line was taken as the pressure in the teat with the bottle in the

position for feeding, that is atmospheric pressure plus the hydrostatic pressure of the column of fluid in the bottle. When the recording tube was outside the teat (bottle or breast) the base line was taken as atmospheric pressure.

Results

The cineradiographs were first compared with those taken on a previous occasion (5 & 6) to find whether the animal (or baby) was taking its food normally. It was found that the tubes fixed to the rubber teat tended to interfere with normal behaviour; in some instances the animal (or baby) refused to feed at all, in others the normal rhythm was not readily established and the amount of milk obtained per movement was small. The relatively rigid polythene tubes seemed to limit the compression of the teat. Only those records in which the animal (or baby) appeared to be behaving nearly normally were studied.

Lambs Bottle Feeding

When the lower jaw and the tongue were raised, the lumen of the teat was narrowed and there was a rise of pressure within the neck of the teat reaching a maximum of about 200 mm Hg as the lumen of the neck was occluded (Fig. 1, A, B, C, and Fig. 2). As the tongue indented the bulb of the teat and the contents of the bulb passed into the mouth, the pressure within the bulb towards the neck rose to about 40–50 mm Hg, whereas the pressure in the tip of the bulb only rose to about 20 mm Hg (Fig. 1, C, D, E, F, G, and Fig. 3). When the jaw and tongue were lowered and the teat refilled, the pressure near the neck end of the bulb fell towards the base line, whereas the pressure in the tip of the bulb fell to about –20 mm Hg rising again towards base as the bulb completely filled (Fig. 1, H, J, K, and Fig. 3). The pressure in the mouth im-

mediately beyond the end of the teat varied from about atmospheric to –150 mm Hg as the back of the tongue was lowered, the lowest pressure in the mouth coinciding with the highest in the teat (Fig. 1, I, J, K, L, and Fig. 4). The pressure in the mouth started to fall as the pressure in the teat started to rise. The lowest pressure in the teat was reached just before that in the mouth reached atmospheric, i.e. just before the bulb was completely refilled (Fig. 4). In an experiment with a hard rubber teat in which the cineradiographic films showed only a small deformity of the bulb the pressure in the bulb did not rise to more than about +12 mm Hg or fall to below –12 mm Hg; the lamb appeared to be feeding vigorously but the cineradiographic films showed that the jaws were not closely approximated and he obtained only small quantities of milk.

When the back of the tongue was lowered, and as milk passed from the teat into the mouth, the pressure recorded at the outer surface of the end of the bulb fell from atmospheric pressure (or a few mm Hg above) to approximately –150 mm Hg (Fig. 1, I, J, K, and Fig. 4), returning towards atmospheric pressure as the tongue was elevated to the palate to displace the bolus from the mouth (Fig. 1, C, D, E, G, and Fig. 4). Most attempts to record pressures in the mouth beyond the end of the teat failed, as the animal refused to feed properly.

When the cineradiographs were compared with the simultaneous pressure records it was found that the amount of milk taken into the mouth at different phases of the suckling act varied with the type of teat and the particular animal and was not always directly related to the height of the pressure gradient. Thus in some instances milk passed readily into the mouth when the difference in pressure between the teat and the mouth was relatively small e.g. +15 to –15 mm Hg; conversely, the amount obtained, when there was a considerable difference in pressure, was sometimes small.

On one occasion a lamb took the teat across its mouth, the end of the bulb pre-

Fig. 1. Taking air into the mouth and noesophagus. A. 7. Separation of the bolus from the teat. B-E. Backward movement of the bolus. F-H. Refilling of the teat. I-L. Tongue in the teat.

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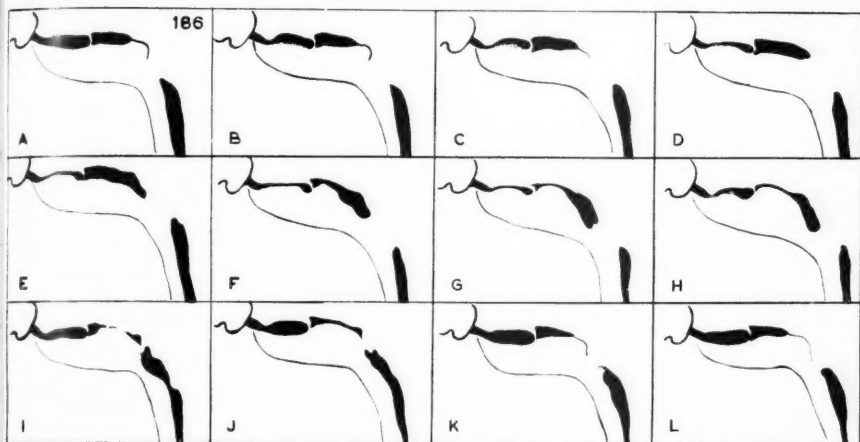


Fig. 1. Tracing taken from alternate frames of a film exposed at 100 frames per second, of a lamb taking barium milk suspension from a bottle fitted with a soft veterinary teat with an incorporated air inlet valve. The tracing illustrates one complete cycle, the duration of which is 0.25 sec. The neck of the bottle is outlined in the top left hand corner of the frame: the skin covering the lower jaw and neck is also outlined. The dense black shadows indicate barium in the teat, mouth, pharynx and oesophagus.

A. The teat is full. There is a large collection of barium in the mouth behind the apex of the teat separated from the former by the thickness of the rubber of the teat. A trace of barium indicates the apposed dorsal surface of the tongue and soft palate. A previous bolus is being expressed from the lower pharynx into the oesophagus.

B-E. Narrowing of the lumen of the teat by progressive elevation of the tongue from before backwards with displacement of most of the contents of the bolus into the back of the mouth. Simultaneously, the back of the tongue is lowered.

F-H. Progressive apposition of the tongue to the hard palate behind the end of the teat is displacing the bolus into the pharynx. Lowering of the forepart of the tongue and low jaw (H) is allowing some refilling of the teat.

I-L. Displacement of the bolus from the pharynx into the oesophagus. Further relaxation of the tongue and jaw is allowing further filling of the teat and reformation of a collection of barium behind the teat.

truding from the side of the mouth in the diasternal region. When it commenced feeding movements jets of milk were observed to spurt across the room.

Babies Bottle Feeding

There were many variations in the behaviour of babies feeding from a bottle. Because of difficulties in sterilisation it was necessary to fix the polythene tube to a teat before the baby's visit to the laboratory; it was impossible to use the baby's own teat and it was not considered advis-

able to use an old one previously discarded. Various proprietary brands of teat were used: in most instances the baby did not feed as well as with its own teat. Attempts were also made to persuade babies to feed from a bottle with a soft rubber teat (made in the laboratory) comparable to the type used for feeding lambs but with these teats there were only a few successful experiments.

When the baby accepted a soft rubber teat the pressure changes were comparable

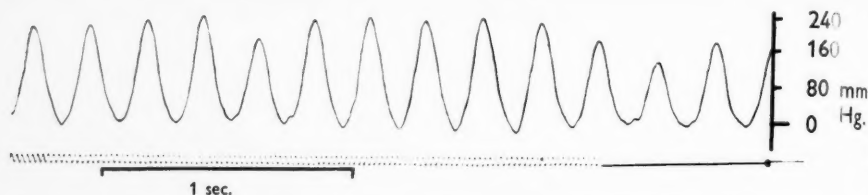


Fig. 2. Lamb bottle feeding: a pressure recording from inside the neck of the teat. The pressure varies between base and about 200 mm Hg. The lower tracing records the cineradiographic exposures at 50 frames per second.

to those obtained when feeding the lambs, a positive pressure up to 40 mm Hg in the bulb of the teat as the neck was occluded with a negative pressure down to -80 mm Hg in the mouth. When the teat was too rigid for its lumen to be obliterated (a proprietary brand) the pressure within the bulb never varied by more than few mm Hg above and below the base pressure; none of the babies succeeded in occluding the neck of the harder types of teat: when the bulb of the teat was indented by the tongue the milk was mainly expressed backwards into the bottle.

As in the lamb the amount of milk obtained was not always related to the

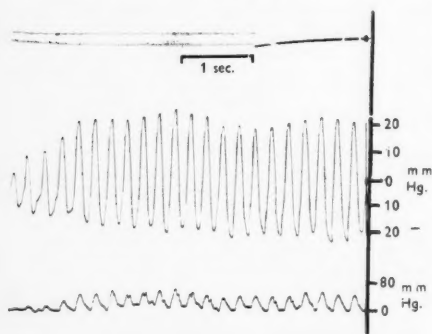


Fig. 3. Lamb bottle feeding. Upper tracing records cineradiographic exposures. Middle tracing records pressures inside the bulb tip of the teat. Lower tracing records simultaneous pressures within the bulb of the teat towards the neck end. Note that the scale of the lower tracing is one eighth of the middle tracing.

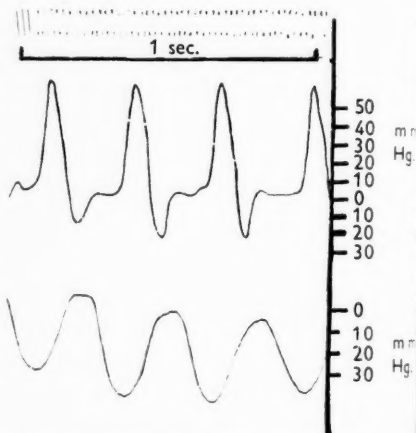


Fig. 4. Lamb bottle feeding. Upper tracing records the cineradiographic exposure. Middle tracing records the pressure in the bulb of the teat. Lower tracing records pressure in the mouth just beyond the end of the teat; the scale is one eighth that of the middle tracing.

height of the pressure gradient across the teat. Many children when taking milk from a bottle fitted with a rigid teat obtained the milk when the pressure in the mouth was either atmospheric or a little below. In one instance a pressure as low as -200 mm Hg was consistently recorded in the mouth but the child obtained only very small quantities of milk from the teat. It appeared that a high pressure gradient was indicative of an inadequate hole in the teat and not of a good flow of milk into the mouth.

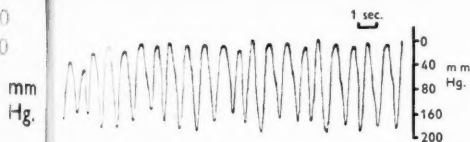


Fig. 5. Baby suckling at the breast: pressure recorded in the mouth near the end of the nipple. The upper tracing indicates the duration of the cineradiographic examination. The lower tracing shows that with each feeding movement the pressure varied between atmospheric and -200 mm Hg.

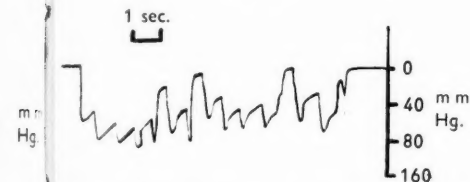


Fig. 6. Baby suckling at the breast-feeding well established. Pressures varied between atmospheric and -150 mm Hg, seldom returning to base between each feeding act.

Babies Breast Feeding

The position of the end of the tube in relation to the teat formed from the mother's breast varied; there was none where the end of the tube was in the position of the neck of the teat. No attempt was made to record the pressure changes associated with the act of taking the nipple into the mouth. When suckling was established, as the end of the nipple was moved backwards in the mouth the pressure usually fell to about -150 mm Hg—the lowest pressure recorded was -250 mm Hg (Fig. 5). As the end of the nipple was displaced forward the pressure rose to about atmospheric and to never more than -3 mm Hg. In many babies there were periods when the pressure never returned to atmospheric (Fig. 6). After some minutes of feeding the pressure did not fall so low as it did initially and peaks of positive pressure appeared more frequently.

Discussion

The results obtained in this investigation are in keeping with the deductions derived from our previous cineradiographic observations (5 & 6). The cine films show that the rhythmical tongue and jaw movements whereby the baby (or animal) obtains milk from the bottle may be divided into two components. First, he compresses the teat between the tongue and the hard palate. This is only effective if the neck can be occluded between the jaws, if the bulb can be indented by the tongue and if the hole in the teat is sufficiently large. Secondly, as the forepart of the tongue is raised to indent the bulb of the teat the tongue behind the teat is lowered so tending to create suction in the mouth behind the teat: by this means or by gravity alone the child may obtain an adequate supply of milk even if the teat is made of rigid material provided the hole is large enough. Both methods are attempted by babies (and animals); if the teat is unsuitable only the latter method can be used. When these methods are efficiently coordinated, as in the lamb, a mouthful of milk can be taken and swallowed with each feeding movement.

The artificial teats usually supplied for human babies are not soft enough for the baby to occlude the neck of the teat: the baby's tongue usually indents the bulb of the teat but as the neck is not closed most of the contents of the bulb are displaced backwards into the bottle. The average baby cannot express the contents of the bulb until its teat is old and softened.

The fact that the contents of the bulb may be expressed is confirmed by our observation of the lamb who took the teat across the mouth with its tip protruding

from the opposite side and who expells jets of milk across the room with each cycle of jaw movement. Likewise it has also been shown that the lamb can obtain a supply of milk by suction from a bottle placed on the floor when the teat is fixed to a tube reaching close to the bottom of the bottle (4 & 5).

The object of the investigation was to measure the pressure relationships. We have to admit that the conditions under which these examinations were conducted were not ideally suited for exact physical measurements under physiological conditions. It has been emphasised that none of our babies behaved entirely normally, since the cine films showed that the relatively rigid polythene tubes sometimes interfered with the occlusion of the neck and the flexibility of the bulb of the teat. In many experiments with teats with the same sized hole it was obvious that the effective size of the hole varied. That we could not easily persuade babies to take the soft rubber teat for our purpose is no indication that soft teats are not acceptable to babies; for we have previously determined that the baby will not take a soft teat or any other kind of strange teat unless gradually accustomed to use it, and likewise lambs who normally take a soft teat will not readily accept a hard teat.

From general physical principles it follows that the flow of milk into the mouth is conditioned by the forces applied, the duration of their application and their rate of change, the physical characteristics of the hole in the teat and the viscosity of the milk. If the forces applied and viscosity of the milk remain constant the difference in pressure between the interior of the bulb of the teat and the mouth cavity will

be greater the smaller the hole, or conversely, the larger the hole the smaller will be the difference in pressure.

In the lamb we have previously shown that the amount of milk obtained during the phase of expression of the contents of the bulb by the tongue is approximately equivalent to the amount of milk which flows into the back of the mouth when the tongue is lowered to allow the bulb to be refilled. In this investigation we have found that the phase of expression is associated with a rise of pressure in the bulb of the teat and a fall of pressure in the mouth; and when the bulb of the teat refills the pressure at the back of the mouth rises towards atmospheric.

We have also seen that if the hole in the teat is large enough a small pressure change between the interior of the teat and mouth cavity is sufficient to produce an adequate supply of milk: this may be partly determined by the height of the fluid in the bottle, the equivalent of 5-15 mm Hg positive pressure at the level of the lips when the bottle is full; conversely a relatively high degree of vacuum in the mouth is by no means invariably associated with a good flow of milk.

The size of the hole in the teat is very important. In many records it was obvious that the hole in the teat was too small (even though we had no means of measuring its effective size) when there was a relatively high degree of vacuum in the mouth associated with a poor flow of milk: a relatively high vacuum can only result when the tongue is drawn away from the palate at such a rate that the cavity produced is not readily filled or in other words when the hole is too small: no help can be obtained from the pressure exerted by the forepart of the tongue upon the bulb of the teat unless the neck of the teat is significantly nar-

rowed or occluded: in our records there was only a very slight rise of pressure inside the teat when the neck was not narrowed.

In experiments with a baby's open ended bottle fitted with a teat as sold by the manufacturer (diameter of hole approximately $20/1000''$) it was found that a column of milk 22 cm high allowed milk to drop out at a rate of 15 ml per minute. When the size of the hole in the teat was enlarged with a needle to a size roughly corresponding with the maximum size employed clinically (approximately $26/1000''$), the rate of flow was 28 ml per minute. Assuming that the child takes as long to take milk as to swallow it we calculate that with a small hole the child can take a feed of 142 ml in 20 minutes if it can maintain the pressure gradient from teat to mouth of approximately 20 mm Hg. Whereas with a large hole the same feed with the same pressure gradient should be consumed in about 10 minutes. If the bottle were not open ended the tendency to create a vacuum in the bottle would reduce these flow rates.

The mechanism of breast feeding is probably similar to bottle feeding. It has been shown that the changes in form of the cavity of the teat sinus of a goat's teat during suckling are analogous to the changes in form of the lumen of a soft rubber veterinary teat when the kid is being bottle fed: the nanny's nipple is soft enough to allow the kid to occlude the neck of the teat sinus between the jaws to express the contents with its tongue; the pressure relationships between the teat sinus and the mouth have been shown to be similar to those described above during bottle feeding (2 & 3). The size and changes

in form of the lumen of the mammary ducts in a woman's breast during suckling are not known, but we have shown that the baby forms a teat from its mother's nipple and breast, analogous in appearance (externally) to that formed by the kid goat from its nanny's teat (6): it may be that the combined capacity of the lumen of the ducts of a woman's nipple is comparable to that of a nanny's teat sinus, and the changes in form during suckling may be similar. The changes in the form of the lumen of the cow's teat when milked by a milking machine is not analogous to that seen in natural suckling (1).

Gunther (9) who considers that the babies gums, lips and tongue work on the yielding tissues of the breast behind the nipple beneath the areola, has measured the protractility of the breast tissues (elongation) when a pressure of -60 mm Hg was applied to the nipple. She found that in 150 women the protractility varied from 2 to 3.75 cm: of those women who offered a length of 2.75 cm or more there were few who were unsuccessful in feeding their babies compared with the number of failures of those whose protractility was less.

No one has yet measured the range of pressures existing between the lumen of the lacteal sinuses of the human breast and the mouth of the child during suckling. It is known that stimulation of the nipple results in a rise of pressure within the breast by exciting the milk ejection reflex (7), and this may often produce a jet of milk from the breast.

Tgetzel (15) who studied the lactation of the cow published a graph showing the alteration of pressure within the udder; the pressure within the udder rose steadily for

about eleven hours after milking to approximately 20 mm Hg; when the milk ejection reflex was excited at intervals of 3 and 7 hours after milking there was a further rise of pressure of about 10 mm Hg which subsided when the stimulus was removed. Krzywanek & Bruggeman (10) who studied 33 cows found an average pressure of 49 mm Hg rising to an average of 67 mm Hg after exciting the milk ejection reflex; there was a wide range of pressures varying from 25 mm rising to 60 mm Hg, to 80 mm Hg rising to 90 mm Hg.

The pressures in the mouths of calves during suckling from artificial nipples have also been measured by Krzywanek & Bruggeman (11) who found variations from 50 mm Hg to 290 mm Hg; they expressed the opinion that negative pressure developed by calves suckling their specially constructed nipple was greater than that which would occur in normal nursing. Martjugin (12) who studied 5 calves suckling from an artificial teat distinguished two alternative phases—one in which there was a fall in pressure in the mouth to -142 mm Hg and a pressure on the teat ranging from -38 mm to 102 mm which he attributed to suckling, and a second phase in which the pressure on the teat ranged from $+6$ mm to $+166$ mm Hg with a negative pressure in the mouth ranging from zero to -70 mm Hg which he attributed to swallowing; Smith & Petersen (14) who also studied this problem in a similar manner found that the lowest negative pressure in the mouth developed by calves suckling from artificial nipples ranged from -305 to -456 mm Hg as compared with -229 to -405 mm Hg negative pressure when the same calves suckled cows. The significance of these investigations is difficult to assess since it is apparent that none of the authors had any means of observing the pressure changes in relation to the different phases of tongue movement, nor did they know at what phase the calf obtained milk.

The degree of vacuum measured in the mouth of calves in the above mentioned

experiments though higher is in agreement with our findings in lambs and in human babies when feeding from the bottle or from the breast. Our findings confirm those of Gunther (8) who showed that pressures in the mouth of suckling babies varied from a little above atmospheric to -200 mm Hg. She also noticed that sometimes a negative pressure of about -70 mm Hg was sustained for several minutes without evidence that the child was swallowing. Why so much negative pressure should be created in the mouth is not certain.

In bottle feeding we have found that a considerable quantity of milk may enter the mouth before the lowest pressure is reached: it may be that the production of negative pressure in the mouth is primarily a factor of a rapidly moving tongue when the tongue is lowered to allow the bolus to move to the back of the mouth as the tongue is raised in the forepart of the mouth immediately before swallowing.

The action of the tongue in expressing the contents of the bulb of the rubber teat into the mouth is exactly analogous to that of the tongue in displacing a bolus backwards from the forepart of the mouth in the first stage of swallowing (4); no one now disputes that swallowing is primarily due to a positive thrust exercised first by the tongue and then by the constrictors of the pharynx. The act of suckling can also be likened to swallowing in another respect; when drinking quickly the airway is not restored after swallowing the first mouthful of fluid so that the lowering of the back of the tongue and the opening of the pharyngeal cavity to receive the second bolus must tend to create suction which must aid the pos-

itive thrust of the tongue. In both sucking and swallowing there is alternate raising and lowering of the front and back of the tongue.

Pier, Schalm & Hage (13) have shown that a negative pressure of -305 mm Hg exerted by a milking machine applied to a limited area of human skin will result in damage to the tissues. Gunther (8) showed that a pressure of 100 mm Hg applied for two minutes to the skin of the arm produced petechiae in 38 out of 59 mothers tested; she considered that the position of the petechial lesions on the breast of nursing mothers and the strong sustained suction created by their babies indicates that suction unreleased by swallowing is the main cause of petechial haemorrhages. This is the reason why in dairy farming the type of milking machine which depended on a constant vacuum had to be abandoned.

The cineradiographic appearances of the mouth of an adult when sucking through a straw have been previously described (4). Pressure recorded in the mouth of an

adult sucking fluid through a straw have many points of similarity with those obtained just beyond the end of the teat in the mouth of lambs or babies bottle feeding and in the mouth of children breast feeding.

Why an animal or baby takes the teat into the mouth or forms a teat from its mother's breast is still not clear. We have previously pointed out that it should only be necessary for the baby to take the teat between the lips if suction was the only method of obtaining milk from the breast. With the teat in the mouth the animal looses an equivalent volume which could be used by the tongue to exert suction and to accommodate milk. It may be argued that with the teat in the mouth the baby can obtain a better hold on the breast but in the human this seems to be a rather specious argument since the human breast is so formed as to be particularly well suited for the application of the baby to the breast if only the nipple had to be taken between the lips for suction (16).

Summary

A cineradiographic analysis of the movements of the tongue and jaw in suckling and breast feeding has been previously described: the pressure changes in the teat and mouth of lambs and babies bottle feeding and in the mouth of babies breast feeding have now been correlated with these movements.

1. When the neck of the teat was occluded and the contents of the bulb were displaced into the mouth there was a rise of pressure in the bulb (the maximum rise was about 50 mm Hg); if the neck of the teat was not narrowed or occluded there was little rise of pressure in the teat.

2. As the teat refilled with milk the pressure in the bulb fell a little below the base level, the lowest pressure being reached just before the bulb was completely refilled.

3. There was a fall of pressure (down to -250 mm Hg) in the mouth near the tip of the teat: the lowest pressure in the mouth coinciding with the maximum pressure in the teat; and at this phase there was lowering of the tongue behind the end of the teat and a flow of milk from the teat into the mouth.

4. The pressure in the mouth just beyond the end of the teat usually rose towards the base level as the teat refilled. Near the end of this phase the teat was again full and some milk passed into the mouth; the pressure in the mouth was then in most instances close to atmospheric but in others some degree of negative pressure was sustained.

5. It was shown that a steep pressure gradient between the bulb of the teat and the mouth was not necessarily associated with a good flow of milk. If the hole in the teat was large enough a pressure gradient of about 20 mm Hg seemed adequate for normal feeding.

6. The pressure in the mouth adjacent to the end of the nipple during breast feeding was similar to the pressure in the mouth near the end of the teat when bottle feeding.

Etude des rapports entre les variations de pression durant la tétée et les mouvements de la langue.

Une analyse cinéradiographique des mouvements de la langue et des joues durant la tétée au biberon et au sein a déjà été décrite dans une communication antérieure: les modifications de pression à l'intérieur de la tétine et de la bouche d'agneaux et de bébés nourris au biberon ainsi que dans la bouche de bébés nourris au sein se trouvent ici mises en rapport avec ces mouvements. 1) Au moment de l'occlusion du col de la tétine et du passage du contenu de cette dernière dans la bouche, on observe une augmentation de la pression dans le bout de la tétine (l'augmentation la plus forte fut d'environ 50 mm Hg); lorsqu'il n'y a pas de rétrécissement ou d'occlusion du col de la tétine, l'augmentation de la pression à l'intérieur de cette dernière est minime. 2) Au moment où la tétine se remplit à nouveau de lait, la pression dans le bout de la tétine tombe légèrement en dessous de son niveau de base avec un minimum qui se situe juste avant que le bout de la tétine ne soit rempli complètement. 3) Il se produit une chute de la pression (jusqu'à -250 mm Hg) dans la bouche au voisinage de l'extrémité de la tétine et le minimum de pression dans la bouche coïncide avec le maximum de pression dans la tétine; à ce moment également, la langue s'abaisse derrière l'extrémité de la tétine et un jet de lait s'écoule de la tétine dans la bouche. 4) Au moment où la tétine se remplit de lait, la pression dans la bouche au voisinage immédiat de l'extrémité de la tétine, s'élève et remonte habituellement à un niveau supérieur à son niveau de base. Vers la fin de cette phase, la tétine se trouve de nouveau remplie et une certaine quantité de lait passe dans la bouche; à ce moment, la pression dans la bouche est généralement très voisine de la pression atmosphérique, mais il arrive aussi qu'elle reste négative dans certains cas. 5) Il est apparu qu'une forte différence de pression entre le bout de la tétine et la bouche ne va pas nécessairement de pair avec un bon écoulement du lait. Lorsque l'orifice de la tétine est suffisamment large, une différence de pression de l'ordre de 20 mm Hg paraît être adéquate pour une alimentation normale. 6) Chez les enfants nourris au sein, la pression régnant dans la bouche au voisinage de l'extrémité du mamelon est comparable à celle que l'on observe dans la bouche au voisinage de l'extrémité de la tétine chez les enfants nourris au biberon.

Über die Beziehung zwischen den Druckhöhen beim Säugen und den Zungenbewegungen.

Eine kineradiographische Analyse der Zungen- und Kieferbewegungen beim Säugen und bei der Brusternährung wurde vorher beschrieben; Die Druckschwankungen im Schnuller und dem Mund bei Lämmern und der Mundhöhle von mit der Flasche und an der Brust ernährten Säuglingen sind in Beziehung zu diesen Bewegungen gebracht worden. 1) Wenn man den Hals des Schnullers zudrückte und den Inhalt aus der Kugel des Schnullers in die Mundhöhle überfließen liess, stieg der Druck in der Kugel an (bis zu einem Maximum von etwa 50 mm Hg); wenn der Hals des Schnullers wieder verengt noch versperrt wurde, stieg der Druck im Schnuller nur wenig an. 2) Wenn der Schnuller sich wieder mit Milch auffüllte, fiel der Druck in der Kugel ein wenig unter den Grundwert ab, wobei der niedrigste Druckwert gerade, bevor die Kugel gänzlich ausgefüllt war, erreicht wurde. 3) Ein Druckabfall (bis zu -250 mm Hg) wurde in der Mundhöhle in der Nähe der Spitze des Schnullers verzeichnet; der niedrigste Druck in der Mundhöhle fiel zeitlich mit dem höchsten Druck im Schnuller zusammen; in dieser Phase trat eine Senkung der Zunge hinter dem Endteil des Schnullers ein und Milch floss aus dem Schnuller in die Mundhöhle. 4) Der Druck in der Mundhöhle hinter dem Endteil des Schnullers stieg gewöhnlich zum Grundwert an, wenn sich der Schnuller wieder auffüllte. Gegen

das Ende dieser Phase zu war der Schnuller wieder voll und etwas Milch trat in die Mundhöhle über; der Druck in der Mundhöhle war dann in der Mehrzahl der Fälle dem atmosphärischen nahe, aber in manchen Fällen dauerte ein gewisser negativer Druck an. 5) Es wurde gezeigt, dass ein steiles Druckgefälle zwischen der Kugel des Schnullers und der Mundhöhle nicht notwendigerweise mit einem guten Milchzufluss verbunden war. Wenn das Loch im Schnuller gross genug war, war ein Druckgefälle von ungefähr 20 mm Hg für normale Ernährung anscheinend hinreichend. 6) Der Druck in der Mundhöhle unmittelbar neben der Brustwarze bei der Brusternährung war dem Druck im Munde neben dem Schnullerendteil bei Flaschenernährung ähnlich.

La correlación entre las presiones de lactación y los movimientos de la lengua.

El análisis cineradiográfico de los movimientos de la lengua y mandíbula ha sido previamente descripto. Los cambios de presión, en la tetina del biberón y en la boca, de corderos y lactantes criados con biberón, y en la cavidad bucal de lactantes alimentados a pecho directo, son ahora correlacionados con aquellos movimientos. 1) Cuando el cuello de la tetina fué ocluido, y el contenido del bulbo desplazado hacia la boca, se registró un aumento de presión en el interior del bulbo (aumento máximo de aproximadamente 50 mm Hg). Si el cuello de la tetina no era estrechado u ocluido completamente, el incremento de presión en la tetina era pequeño. 2) Cuando la tetina es nuevamente llenada con leche, la presión en el bulbo cae un poco por debajo del nivel basal, siendo la presión más baja alcanzada inmediatamente antes del lleno del bulbo. 3) Hay una caída de la presión (por debajo de -250 mm Hg) en la zona de la boca próxima a la punta de la tetina. La presión más baja en la boca coincide con la presión máxima en la tetina, en esta fase se registra un descenso de la lengua detrás del extremo de la tetina y un aflujo de leche desde el biberón hacia la cavidad oral. 4) La presión en la boca, un poco más allá de la terminación de la tetina, sube usualmente hacia el nivel basal con el relleno de la tetina. Cerca del final de esta etapa, la tetina se encuentra nuevamente llena, y un poco de leche pasa a la boca. La presión de la boca en este momento, es en la mayoría de los casos próxima a la atmosférica, pero a veces se registra cierto grado de negatividad. 5) Se demostró que un acentuado gradiente de presión, entre el bulbo de la tetina y la boca, no está necesariamente asociado con un buen aflujo de leche. Si el orificio de la tetina es lo suficientemente grande, un gradiente de presión de 20 mm de Hg parece ser adecuado para una alimentación normal. 6) En niños amamantados a pecho, la presión intrabucal, en la zona adyacente al cabo del pezón, es similar a la hallada cerca de la tetina en los amamantados a biberón.

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Nuffield Institute for Medical Research
University of Oxford
Oxford, England

CASE REPORT

Case of Pulmonary Nocardiosis with Recovery

by RENÉE FONÓ and ANNA CSILLAG

From the II. Paediatric Clinic, University of Budapest, and the State Institute of Hygiene, Budapest

Pulmonary nocardiosis is one of the rarely occurring and even more rarely diagnosed illnesses. Its pathogen is a microorganism of aerobic type belonging to the actinomycetaceae first described in animals by Nocard (3) in 1888. Two years later, in 1890, Eppinger (2) reported the first infection observed in man. By way of histological examination, he managed to reveal the fungus from the lungs and from the cerebral abscess of the patient. Because of the typical starlike shape of its colonies, he called the pathogen *Cladothrix asteroides*. Since 1934 (Waksman & Henrici (5)) the name *Nocardia* has been generally accepted.

In the following a brief description of the development and recovery of a case of pulmonary nocardiosis will be given.

Case Report

In April 1956 a little girl, H. T., aged five, was admitted to the Clinic with the diagnosis of congenital heart disease. She was operated on one week later for patent ductus and was sent home quite healthy and in very good condition.

Two months after the operation the parents returned with the child because she had had no appetite, had been tired and had coughed the last two weeks.

At that time the little girl's condition was still satisfactory. Cardiac sounds were clear, the pulse was rhythmical, 100/min. No divergence in percussion of the lungs was noticeable; harsh breathing and occasionally coarse rales were heard. The breathing was steady, 20/min. Liver and spleen were not enlarged. Nervous system, without comment.

Tuberculin test (Mantoux 1/1000) negative. Blood S.R. 10 mm/hour. Erythrocytes 4400.000, haemoglobin 12.6 g%, haematocrit 40. Leucocytes 6800, polynuclears 47%, eosinophiles 2%, basophiles 1%, monocytes 4%, lymphocytes 46%. Blood pressure 115/75 mm Hg. Urine normal. The X-ray picture of the chest revealed a considerable enlargement and elongation of the right hilum (Fig. 1).

During the five-day clinical observation the child was free of fever, had good appetite and coughed but a little. The tuberculin test being negative and the erythrocyte sedimentation normal, she was sent home with instructions for adequate rest and to return within a few weeks.

The little girl reappeared, however, three months later in September, 1956. According to her mother, since her last clinical stay she had had slight fever, had been coughing, and did not seem to be healthy.

The child had lost 3 kg, her face was pale with dark shadows under her eyes, and her lips were cyanotic. The breathing was heavy and rapid, 36/min. On both sides of the chest crackling crepitations could be heard. Liver and spleen were palpable.

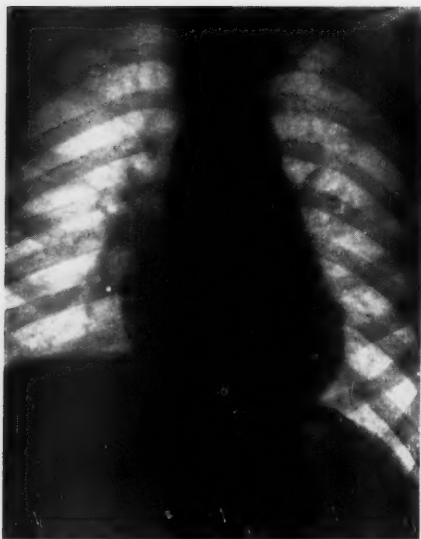


Fig. 1.

Tuberculin test negative. Sedimentation rate 35 mm h. Erythrocytes 4000,000, haemoglobin 12.5 g%, haematocrit 40. Leucocytes 50,000, polynuclears 27%, eosinophiles 6%, basophiles —, monocytes 3%, lymphocytes 64%.

Myelogram: Promyelocytes 3%, myelocytes 20%, metamyelocytes 6%, polynuclears 42%, eosinophiles 14%, basophiles 1%, lymphoid reticulum cells 1%, plasmodioid reticulum cells 1%, megacaryocytes 1%, lymphocytes 8%, monocytes 3%. Erythropoiesis normal.

The X-ray picture showed serious lesions. The hilum on both sides was considerably enlarged. In the lungs were scattered innumerable spot-like shadows the size of pinheads or even larger. In the right upper lung and medially above the diaphragm the scattering was so dense that the small confluent spots formed larger non-homogeneous shadows (Fig. 2).

The lack of appetite that had lasted for some months, the loss of weight, the coughing, and the lesions shown to be more and more extensive by X-ray, suggested some chronic pulmonary disease of unknown

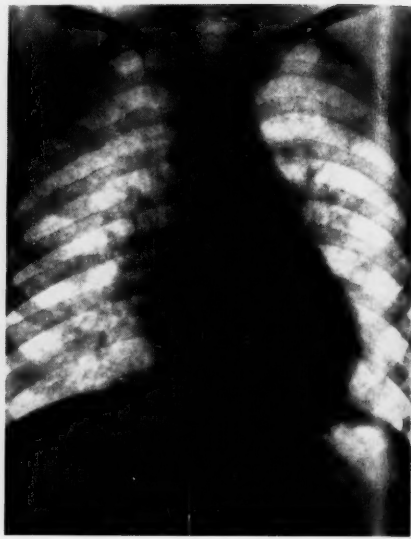


Fig. 2.

origin. The latent outbreak with vague symptoms, and the relatively slow progress contradicted a disseminated bronchopneumonia. The absence of fever in the beginning, the normal erythrocyte sedimentation rate, and the consistent negative tuberculin tests made tuberculosis improbable.

Due to the unusual and slow progress as shown by X-ray pictures, there arose the possibility of a fungous infection. A histoplasmin skin-test was carried out, but proved to be negative.

In order to establish the diagnosis of the supposed fungous infection, bronchoscopic examination was performed, and the greenish mucus obtained was sent to the Institute of Public Health for analysis. In the smear made from the mucus, *Nocardia* was found, confirmed by culture.

During the period of culture and identification the child's condition kept declining from day to day; her temperature became higher, cyanosis and dyspnoea increased, and the child suffered from a tormenting cough. Also the X-ray picture of the lungs became more and more serious (Fig. 3). For this reason, without awaiting the results of the

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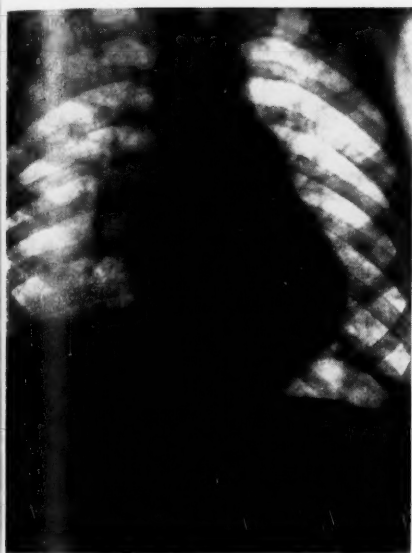


Fig. 3.

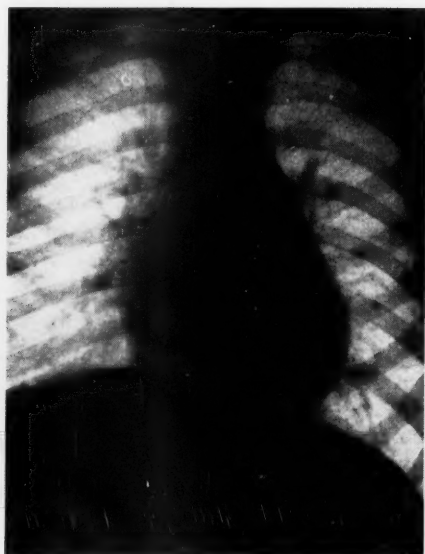


Fig. 4.

culture, a sulphadiazine treatment was started. For two months the child was given 3.0 g sulphadiazine daily. In the first two weeks of the treatment the little girl's condition was unchanged, though from this time on a slow recovery became noticeable. Within three weeks there was no more fever; dyspnoea and cyanosis gradually diminished and within a month ceased to exist. At the same time both the erythrocyte sedimentation and the blood picture became normal. After two months' treatment the X-ray picture of the lungs showed considerable improvement: both hila became broadened and fasciculated. The miliary-like spreading disappeared and only some shadows remained, which were of less density and larger size.

The child recovered and has remained healthy. The X-ray picture 6 months after discharge shows no other lesion besides the enlarged and fasciculated hilum (Fig. 4).

Discussion

The majority of cases in the literature refer to adults, whereas the number of

cases observed in children is insignificant. In 1954 Stadler (4) published one case of a 15-month-old child, where the diagnosis of lung nocardiosis was established only at post mortem. In 1957 Ballenger & Goldring (1) found 96 cases described in the world literature out of which 12 cases had occurred in childhood. In most of these cases the illness had been diagnosed only at necropsy. Clinically diagnosed cases were relatively scarce.

In most cases of nocardiosis the primary infection occurs in the lungs, and other parts of the body (central nervous system, bones, skin etc.) are usually sites of secondary invasion.

In our case the question arises as to how the infection occurred. It may be supposed that the infectious agent had entered the lungs in connection with the operation. The Magill tube used for the intratracheal anaesthesia was not steri-

lized, only mechanically cleaned, and so it is possible that *Nocardia* entered the lungs this way. Previous to the operation the X-ray picture showed lesions characteristic only of patent ductus. Two months later the enlarged hilum indicated the beginning of the disease, and from this time onward, the child's condition and the X-ray picture of the lungs steadily deteriorated.

The child's condition improved with the beginning of the sulphadiazine therapy and most of the symptoms and signs disappeared in two months' time.

The clinical findings, the X-ray picture, the culture-test and the effectiveness of the specific therapy shows that the diagnosis of nocardiosis of the lungs was correct.

The results of the elaborate mycologic test (Anna Csillag) are as follows:

From the subglottic mucus mycologic analysis was carried out on seven occasions, while from the mucus taken with the bronchoscope one analysis was performed. In the 2nd, 3rd, and 7th subglottic mucus no bacterium-elements could be traced either with the Schiff-periodine acid leukofuchsin, or by way of Ziehl-Nielsen, or Gram, or Brown-Brenn staining. From the above-mentioned test materials on Sabouraud's glucose-agar, on blood agar, and antibiotics containing peptonic agar neither at room temperature nor at 37°C were microorganisms growing during a 24 days' period of observation.

In the smears made from the subglottic mucus that had been examined on the 1st, 4th, 5th, and 6th occasion, as well as in those made from mucus taken with the bronchoscope, Gridley staining revealed considerably dyed branching threads of different lengths and about one micron in thickness, as well as diphtheroid elements and bacillary formations. Granules were not found. According to the morphologic picture, the observed microorganism had to be taken for *Nocardia*. Since among the *Nocardia* there exist also acid-fast microorganisms, some smears were stained according to Ziehl-Nielsen. The microorganism did not prove to be acid-fast.

From the samples in which the microorganism in question was revealed, the pathogen could be cultured in every case. On Sabouraud's glucose-agar with incubation at 37°C, under aerobic conditions, the first cultures appeared after the eighth day. First they were white, later they became orange-coloured with a plicate and floury surface; the cultures could not be removed from the agar. Microscopic picture: one-micron thick, fine branching mycelia that do not produce fructification organisms and conidia, but break up to coccoids and bacillary formations. Their color corresponds to dyeing properties of the microorganism found in the smears. The culture yielded no acid-fast organisms.

On the basis of the investigation it became evident that the pathogen was of *Nocardia* species, most probably *Nocardia asteroides*. An exact determination of the species was not possible to carry out.

Summary

A child aged five, who had been operated upon for a patent ductus, developed two months after surgery a chronic and progressive pulmonary disease that proved to be pulmonary nocardiosis. The diagnosis of pulmonary nocardiosis could be proved by the following: (1) In smears of bronchoscopic mucus the pathogen was repeatedly revealed and it could also be identified by culture; (2) even with repeated tests other pathogenic microorganisms could not be cultivated; (3) the patient recovered following sulphadiazine treatment.

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Un cas de nocardose pulmonaire avec guérison.

Chez un enfant de cinq ans, opéré auparavant d'un canal artériel de Botal persistant, on constata deux mois après l'intervention une maladie pulmonaire chronique et progressive, qui s'est révélée être une nocardose pulmonaire. L'hypothèse que la nocardose a été le microbe pathogène peut être prouvée par les faits suivants: 1) dans les frottis du mucus bronchoscopique, le microbe pathogène a été démontré à plusieurs reprises et l'on a pu le tracer aussi à l'aide de cultures; 2) même par des tests répétés on n'a pas pu cultiver d'autres microorganismes pathogéniques; 3) le malade guérit après traitement par la sulphadiazine.

Ein Fall von Lungennokardiose mit Heilung.

Ein 5-jähriges Kind, welches eine Operation für Ductus arteriosus persistens überstanden hatte, erkrankte zwei Monate nach dem Eingriff an einer chronischen fortschreitenden Lungenerkrankung, welche sich als pulmonale Nokardiose erwies. Die Annahme, dass Nokardia der Krankheitserreger war, konnte folgendermassen bestätigt werden: 1). In Abstrichpräparaten von bronchoskopisch gewonnenem Schleim wurden die Keime wiederholt beobachtet und konnten auch mit Hilfe von Kulturen eindeutig gemacht werden. 2). Andere pathogene Mikroorganismen liessen sich selbst in wiederholten Untersuchungen nicht kultivieren. 3). Der Kranke wurde auf Sulphadiazinbehandlung wiederhergestellt.

Un caso de nocardiosis pulmonar seguido de recuperación.

Un niño de 5 años que había sido operado por persistencia del conducto arterioso, presentó dos meses después de la intervención, una enfermedad pulmonar crónica y progresiva que se diagnosticó de nocardiosis pulmonar. La hipótesis de patogenidad de la nocardia se demostró por: 1) Se probó repetidamente la presencia del agente patógeno en las extensiones de moco obtenido por broncoscopia, así como por cultivo. 2). No pudieron obtenerse cultivos de otros microorganismos patógenos, aún en pruebas repetidas. 3). El paciente se restableció después del tratamiento con sulfadiazina.

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II. Paediatric Clinic
University of Budapest
Budapest
Hungary

Bilateral Cortical Necrosis of the Kidneys in Infancy

by GUNNAR ESKELAND and AASE SKOGRAND

From the University Pediatric Clinic (Head: Prof. L. Salomonsen) and the Institute of Pathological Anatomy (Head: Prof. O. Torgersen), Rikshospitalet, Oslo, Norway

Bilateral cortical necrosis of the kidneys was first described by Juhel-Rénoy in 1886, in a 16 year old girl suffering from scarlatina. Later, between 200 and 300 cases have been published.

The first description of this disease in an infant was given by Campbell & Henderson (3) in 1949, and from more recent literature we have collected data concerning 23 other cases within this age group.

From Scandinavia only one case occurring in childhood has been reported (23); this is why we have felt justified in recording 2 cases observed in infants less than 1 year old, and in giving a brief survey of the dominant features of this disease.

Etiology and Pathogenesis

Most cases of cortical necrosis of the kidneys occur in connection with pregnancy and childbirth, particularly in cases of abruptio placentae. If pregnancy can be excluded, most cases in adults are connected with acute infections, intoxications, traumatic shock, excessive dehydration, or purpura (6).

In children, cortical necrosis is almost exclusively connected with acute infections: scarlatina (7), sepsis (22), otitis (3, 22), rhinopharyngitis (23), and others. Most often, and especially in infants, the initial disease appears to have been gastroenteritis (3, 14, 22).

In some cases, no definite signs of infection or intoxication can be found, and the cortical necrosis seems to have been occasioned by an operation (3, 19, 22), asphyxia neonatorum (22), melena (13), medicament injections (22), and in some cases no eliciting factor at all can be indicated.

The prevalent opinion is that these necroses result from ischemia, the pathogenesis of which has, however, caused considerable discussion.

Thrombosis of the minor cortical arteries with or without necrosis of the arterial wall, has been registered (2, 5), but these changes are inconstant, and most authors consider them a secondary or insignificant phenomenon (7, 14).

Dilatation of the glomerular capillaries by many authors regarded as the essential feature of the pathogenesis (2, 3, 7). Vascular dilatation leads to increased permeability

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Fig. 1. Case 1. Kidneys (left kidney sectioned), showing mottled gross appearance, and the narrow, pale cortex on cut surface.

hemoconcentration, slow circulation, stasis, in the glomerular tuft, possibly accompanied by the formation of thrombi.—The histological picture (Fig. 3 & 4), as well as experimental investigations, lend support to this theory. By means of injections of staphylococcal toxin in animals, the typical picture of cortical necrosis may be produced, in which the first changes seen are an extreme vasodilatation of afferent vessels and glomerular capillaries (15).

Others (17, 19) believe that a lasting vasoconstriction of the arterioles and glomerular capillaries constitutes the essential factor. After 6–7 hours vasodilatation may occur, but at that time the ischemic injury has already been caused. This hypothesis, too, receives support

from experimental data, as cortical necrosis of the kidneys may be produced by the injection of various vasoconstrictive substances (6).

Actually, these two hypotheses do not diverge very much. It is a well known fact that vasodilatation is the first reaction of the capillaries to ischemia, and the dilatation of the glomerular capillaries may therefore well be regarded as a secondary effect of a strong arteriolar spasm.

Several investigators (6, 14) maintain that the varying histological picture can best be explained as the result of a combination of two or more pathogenetic factors: Vasoconstriction, vasodilatation, possibly also thrombosis and/or necrosis of the vascular walls. An excessive suscep-

tibility of the renal vessels has been postulated to explain those cases where no sign of a primary disease can be found, or to account for the singular phenomenon that some patients are attacked by cortical necrosis of the kidneys subsequent to trivial infections.

Page & Glendening (16) have produced cortical necrosis of the kidneys in rats by injecting serotonin. They put forward an interesting hypothesis concerning the pathogenesis in patients with abruptio placentae: In this condition, thromboplastic proteins escape to the maternal circulation. This results in various degrees of defibrination. Platelet participation in this coagulation process could be expected to release fairly large amounts of serotonin, which may cause necrosis of the renal cortex.—Naturally, it remains to be seen whether this hypothesis will receive support from clinical investigations.

Pathological anatomy

The renal changes vary to a considerable degree according to the intensity and duration of the disease (3, 14, 19, 22). In most cases the kidney surface is mottled, with a mixture of hemorrhagic and light yellow spots. The cut surface presents the same mottled appearance of the cortex. In the event of massive necrosis, the entire cortex is light yellow, frequently with a hemorrhagic border zone and dark radiating lines.

The kidneys are, however, in many instances *grossly normal* (5 out of 11 cases reported by Zuelzer *et al.* (22)). This fact, when seen in connection with the nonspecific symptoms and the fact that oliguria/anuria of short duration often remains un-

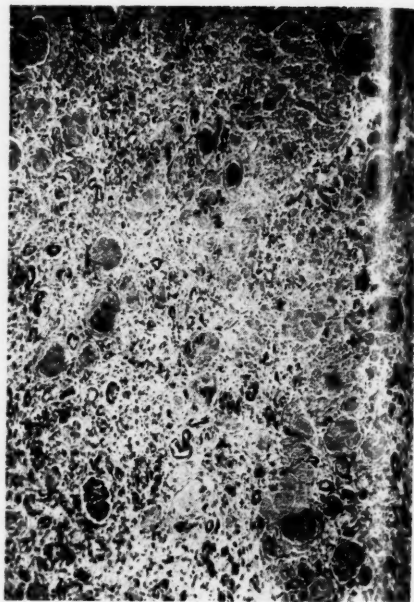


Fig. 2. Case 1. Extensive necrosis of cortical parenchyma. In the lower part one glomerulus and some tubules of fairly normal appearance. ($\times 75$).

discovered in infants, may involve that the diagnosis is not made, even when a post mortem is carried out.

Microscopically, in the massive cases a wide-spread coagulation necrosis is found (Fig. 2), comprising both glomeruli and tubules. Very often, however, a narrow band of intact parenchyma is seen just beneath the capsule, and sometimes the juxtamedullary zone of cortical tissue is also spared. In other cases, more or less confluent necrotic patches are seen surrounded by intact parenchyma, and in the least severe instances, necrotic changes are seen only in the tubular epithelium, the glomeruli remaining unaffected.

A frequent finding is heavy congestion



Fig. 3. Case 1. Necrotic glomerulus, relatively normal distal tubule, and small vein with intense congestion. ($\times 720$).

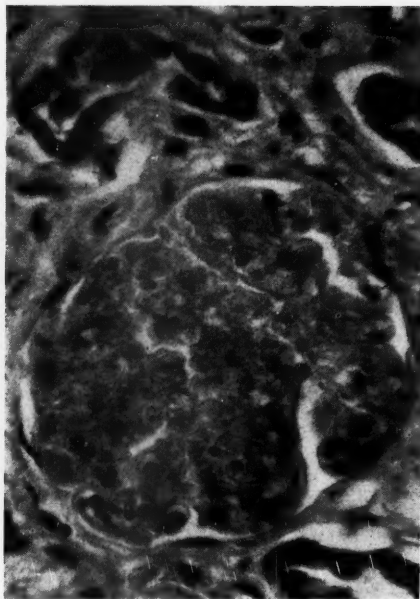


Fig. 4. Case 1. Intense congestion of capillaries in necrotic glomerulus. Tubule showing evidence of regeneration. ($\times 740$).

accompanied by erythrodiapedesis or major hemorrhages. In some cases necrosis of the walls of minor arteries is found, with or without the formation of thrombi.

Peripherally to the necrotic areas infiltrates of lymphocytes or granulocytes are observed. Lesions of an older date often show signs of regeneration of tubular epithelium (Fig. 4.).

The interlobular arteries are generally unaffected, and the picture exhibited by the marrow is fairly normal.

As a rule, cortical necrosis is an isolated phenomenon, but occasionally hemorrhagic necroses are found in other organs as well, particularly in the liver, spleen, suprarenal glands, in the brain, and above all in the intestinal tract (3, 6, 20).

Symptomatology

The cardinal symptom of this disease is an acute anuria or marked oliguria. In adults and older children sudden attacks of lumbar pain have been described (8). The symptoms are otherwise uncharacteristic, and may be ascribed partly to the progressive uremia, partly to the initial disease. As a rule, temperature and blood pressure show normal or slightly elevated values. If urine can be obtained, protein, casts, and red and white blood cells are usually found. In most cases a leucocytosis of no peculiar character is present.

In adults and older children, the sensorium often remains surprisingly clear in spite of advanced uremia (6), whereas in

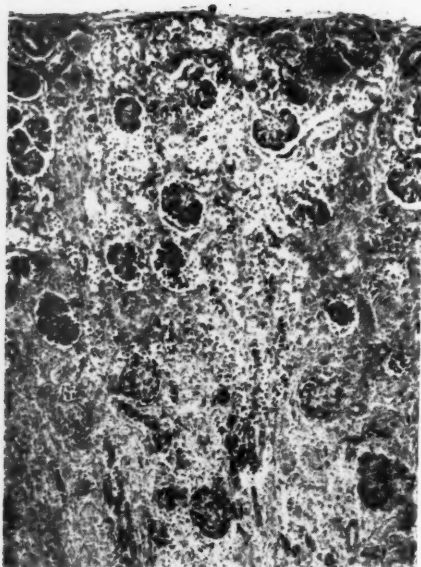


Fig. 5. Case 2. Illustrates the narrow zone with relatively unaffected glomeruli beneath the capsule. ($\times 75$).

infants somnolence or coma is not infrequent (Table 1).

In Table 1, the most frequent symptoms of 26 infants suffering from cortical necrosis are listed. Twenty-four of these cases have been collected from the literature up to 1957, the remaining 2 being our own cases. As will be seen, retching and or diarrhoea constitute the dominant symptoms. Fourteen of the patients had anuria, 5 a pronounced oliguria, whereas in 5 no definite information of the diuresis is given. In 10 patients the values of blood urea have been recorded, being in almost all cases between 200 and 400 mg per 100 ml.

Case Reports

Case 1. A girl of 9 months. In the seventh month of pregnancy her mother had an

attack of pyelonephritis, treated with antibiotics. Otherwise, there were no complications during pregnancy and delivery. The weight at birth was 3100 g.

In the beginning of July, 1957, the girl was vaccinated against smallpox, and went through a seemingly normal reaction post vaccination. She had otherwise been healthy until the onset of the disease in question.

Towards the end of July she developed diarrhoea and a high temperature, and she looked ill. At first she was treated exclusively with strained barley-water and glucose in water, per os.

August 4th, after a few days of recovery, she again developed high temperature and diarrhoea, and was given medicine as follows: August 5th, half a tablet of a sulfa preparation, which she promptly vomited; August 6th, a penicillin injection together with a dose of penicillin syrup that was immediately vomited. August 7th, she was given half a tablet of acetylsalicylic acid.

From August 6th, her stools were brownish black and fluid. On admittance to hospital, August 7th, she had an attack of convulsions, lasting for 45 minutes.

Blood tests gave the following results: Hb. 63%, white cell count 28,000, calcium 9.8 mg per 100 ml, blood urea 135 mg per 100 ml, chlorides 93 meq/L, bicarbonate 12.6 meq/L. A benzidine test in feces was strongly positive.

Urine collected by catheterization gave a strong protein reaction, and contained red and white blood cells and some granular casts. *Later, anuria developed.*

After 2 days of complete anuria she was transferred to the Pediatric Clinic, Rikshospitalet. Temperature: 38.2°C. Blood pressure: 90/40. Laboratory data: Hb 45%, red cell count 2.76 mill., white cell count 40,000, differential count showing a normal distribution. Thrombocytes 150,000, pH in blood 7.20, the alkali reserve 17.6 vol. %. Chlorides 100 meq/L. Potassium 27 mg per 100 ml.

The patient was given penicillin-streptomycin. Otherwise, the treatment aimed at maintaining the water and electrolyte balance. Through a gastric tube she was given

TABLE 1. *Bilateral cortical necrosis. Observations in 26 patients less than 1 year old.*

Sex	Age	Probable initial disease	Vomiting/diarrhea	Dehydration	Convulsions	Cyanosis	Hematemesis/melena	Somnolence/coma	Anuria	Authors
F	5 m.	Gastroenteritis	+				+		+	(3)
M	9 w.	Otitis media	+						+	(3)
M	1 m.	Enteritis	+						?	(20)
M	5 d.	Otitis media	+	+		+	+		+	(22)
M	1 d.	Erythroblastosis	+						+	"
M	3 m.	Cong. heart malformation	+			+		+	+	"
M	7 m.	Ileocolic intussusception					+		?	"
M	7 m.	Otitis media, sepsis	+					+	+	"
F	6 w.	Sepsis	+						Olig.	"
M	2 d.	Imperforate anus, rectourethral fistula	+	+					Olig.	"
M	6 w.	Bronchopneumonia?	+			+			+	"
M	1 d.	Asphyxia neonatorum			+	+			?	"
M	2 m.	Enteritis?	+	+					+	"
F	7 m.	Hemolytic anemia	+						+	(19)
M	7 m.	Gastroenteritis	+						+	"
M	5 m.	Gastroenteritis	+		+			+	+	(14)
M	12 d.	Gastroenteritis?	+	+		+		+	?	"
M	2 m.	Gastroenteritis	+		+			+	Olig.	"
M	7 m.	Enteritis	+		+			+	+	"
M	3 w.	Atelectasis				+		+	Olig.	(1)
M	3 m.	Pancreatic ectopia					+		?	(13)
F	2 m.	Purulent rhinitis	+		+			+	+	(10)
F	7 m.	Thrombotic microangiopathy	+					+	+	"
M	6 m.	Favism	+					+	+	(5)
F	9 m.	Gastroenteritis	+		+				+	"
M	1 d.	Esophageal atresia, op. Adrenal hypoplasia							+	"

Bull-Borst diet and glucose, and intermittently sodium bicarbonate and sodium chloride were administered. Blood transfusions were given as indicated by the hemoglobin values.

After 72 hours of anuria a few ml of urine appeared. Microscopy revealed broad, granular casts and epithelial cells from the kidney. Later, she passed a little urine every day, the amounts increasing up to 36 ml on September 3rd.

The general condition of the infant was unchanged for a long period. She was weak, but the sensorium stayed clear. The blood urea values remained high, varying between 300 and 400 mg per 100 ml. During the last days, her weakness increased, she was con-

stantly retching, developed edema, and had recurrent attacks of tonic convulsions. Death supervened on September 7th, just over a month after the onset of the disease.

Post Mortem Findings

Kidneys: Both kidneys were of a mottled appearance, with a mixture of light, greyish yellow, and dark brown spots. On the cut surface the cortex was found to be reduced to a layer about 1 mm broad, greyish yellow in colour, and containing small areas of a darker shade (Fig. 1).

Microscopically, necrosis of almost the entire cortex was found (Fig. 2). In most areas the necrosis was complete, comprising

all the elements, including the vessels. In other areas the vessels remained uninjured, but glomeruli as well as tubules were more or less necrotic. In several places there were signs of regeneration of tubular epithelium (Fig. 4).

In most areas an extreme congestion of the glomerular capillaries and arterioles was evident (Fig. 3 and 4).

Preserved cortical parenchyma was found only in very limited areas just beneath the capsule, and verging on the marrow. The glomeruli in these areas looked fairly normal, whereas the tubules were dilated, with a flattened epithelium, and with eosinophilic casts in the lumina.

Moreover, the post mortem revealed an intensive fatty infiltration of the liver, and hemorrhages, edema, and minor bronchopneumonic foci in the lungs.

Case 2. Newborn, premature boy. The mother had been healthy during pregnancy, but she gave birth 4 weeks before full term. The weight at birth was 1600 g. Shortly after birth, clinical and x-ray examination revealed atresia of the esophagus, and, 11 hours after birth, the child was operated in the Surgical Department A, Rikshospitalet. Ligature of the esophago-tracheal fistula and reconstruction of the esophagus were performed.

The general condition of the infant was poor prior to the operation, and grew steadily worse, until death supervened 2 days later. *During the last 2 days the patient was anuric.*

Post Mortem Findings

The kidneys were of a dark, bluish red colour, and somewhat mottled. The cut surface showed extensive hemorrhages in the cortex, and hemorrhagic streaks radiating into the marrow as well.

Microscopically, just beneath the capsule a narrow zone was found, in which the cortical tissue looked fairly normal, except for a marked congestion of the capillaries. Small islands of preserved parenchyma were furthermore found in a narrow area bordering on the medulla. Apart from this, there was

an extensive necrosis of the entire cortex, in most places almost complete. The glomerular capillaries and the arterioles were maximally dilated and filled with erythrocytes, and extensive bleedings had taken place. Some hemorrhages had occurred in the marrow as well, but otherwise the medullary parenchyma looked normal.

The post mortem also revealed:

- 1) Competent anastomosis in the esophagus,
- 2) pulmonary atelectasis,
- 3) hypospadias, but no urethral stricture,
- 4) hypoplasia of the adrenal glands, total weight being 1 g.

Microscopically, a well developed adrenal cortex was found. Medullary tissue, giving a normal impression, was found excentrically located, not being enveloped by the cortex.

Diagnosis

As previously stated, the symptomatology of this condition has no special characteristics, being dependent on the degree of uremia and on the initial disease. Clinical examination and laboratory tests give results similar to those found in cases of anuria/uremia resulting from other causes, and the diagnosis can scarcely be made *intra vitam* without a representative kidney biopsy (11).

Differential diagnoses to be considered are, above all, acute glomerulonephritis accompanied by anuria, urolithiasis with anuria, and acute, ischemic anuria (acute tubular interstitial nephritis or "lower nephron nephrosis").

A plain x-ray exposure of the urinary tract is non-contributive; however, it should be performed in an effort to exclude a possible mechanical cause of the anuria.

The Treatment

does not differ from the treatment of anuria resulting from other causes. It

should aim at the maintenance of a normal water and electrolyte balance, being based on the hope that a sufficiently large amount of cortical tissue has escaped injury, so that the renal function may recommence.

Prognosis

All cases occurring in infancy and childhood, and published under this diagnosis, have had a fatal issue. However, it is very probable that cases of partial necrosis of the renal cortex occur, in which reasonable possibilities of recovery may be presumed. The difficulty of reaching the diagnosis *intra vitam* will prevent the reversible cases from being registered under the correct diagnosis, and the prognosis may thus be far less hopeless than suggested by the literature at present.

In pregnant women, reversible cases have been reported, the diagnosis of which may be considered certain (19). Danish

authors (8, 11) have secured this diagnosis in a non-pregnant woman by means of 2 kidney biopsies. The patient survived, and the diagnosis was confirmed by x-ray examination 2 months after the onset of the disease, when tomography revealed diffuse calcinosis of the peripheral zone of the cortex of both kidneys.

Reversible cases of anuria in children have been published under other diagnoses (4). Judging from the descriptions given, we might suppose some of these cases to represent partial cortical necrosis of the kidneys. In one of the cases reported by Zuelzer *et al.* (22), the necroses were of such small extent that the authors thought it probable that a restitution would have taken place, had the child not succumbed to a persistent diarrhoea.

It is impossible, therefore, to form a true picture of the prognosis of this condition, as long as it has not become a routine practice to perform kidney biopsy in cases of anuria of uncertain origin.

Summary

Two cases of bilateral cortical necrosis of the kidneys in infants below the age of one year are reported. A brief survey of this rare disease is given, and various aspects of the condition are discussed.

Nécrose corticale bilatérale des reins chez les nourrissons.

On rapporte deux cas de nécrose corticale bilatérale des reins chez des nourrissons de moins d'un an. On donne un bref rapport de cette maladie rare, et on discute ses aspects divers.

Beiderseitige Nierenrindennekrose im Kindesalter.

Es wird über zwei Fälle von beiderseitigen Nierenrindennekrose bei Kindern im Alter von weniger als einem Jahr berichtet. Ein kurzer Überblick über diese seltene Krankheit wird geboten und die verschiedenen Gesichtspunkte dieses Zustandes werden erörtert.

Necrosis cortical de ambos riñones en la infancia.

Se reportan dos casos de necrosis cortical de ambos riñones en niños menores de un año. Se revisa brevemente esta rara enfermedad, discutiéndose varios aspectos de la misma.

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University Pediatric Clinic
Rikshospitalet
Oslo, Norway

PROGRESS IN PEDIATRICS

Infections with Adenovirus Type 7 in Children and Their Relationship to Acute Respiratory Disease

by GÖRAN STERNER

From the Central Bacteriological Laboratory of Stockholm City (Virological Department: Head: A. Svedmyr; Bacteriological Department: Head: G. Tunevall), The Children's Hospital Samariten (Head: L. Ström), and the Infectious Diseases Hospital (Head: J. Ström), Stockholm, Sweden

Cytopathogenic agents of the adenovirus group were described by Rowe *et al.* (22) in 1953, and shortly afterwards by Hilleman & Werner (7) and Neva & Enders (18) in the United States, and Kjellén (14) in Sweden. Since 1953 Types 1, 2, 3, 5, and 7, as well as a strain not belonging to Types 1-7, 9, or 10 (15) have been isolated in Sweden. The relationship between adenovirus Type 3 and pharyngo-conjunctival fever, described by Bell *et al.* (2), and others (8, 24), has been confirmed by Kjellén, Zetterberg & Svedmyr (16).

Adenovirus Type 7 (AV7) is considered to be responsible for undifferentiated acute respiratory disease and cold agglutinin negative primary atypical pneumonia in adults, especially military recruits (3, 6, 21, 23, 25). From school-children AV7 has been isolated both in Sweden (15, 27) and in England (13, 30), and from younger children as well, down to 7 months of age, in Sweden (15, 26, 27).

Further isolations of AV7 in acute respiratory disease in children have been done. All our AV7-positive cases will be discussed here with reference to their aetiological significance.

Material and Methods

From October 1954 up to and including August 1957, 196 children from 1 month to 15 years old with a fairly even sex distribution were examined for the presence of adenovirus. All had acute respiratory infections, from a common cold to severe bronchopneumonia.

All but one of the children were observed while hospitalized in the Children's Hospital Samariten (123 cases) or the Infectious Diseases Hospital in Stockholm (72 cases). Most of them were examined during the disease for which they were admitted, but 31 were investigated because of respiratory disease contracted during their hospitalization; a cross-infection with adenovirus was considered possible.

During the first half year of investigation our interest was focussed on some 50 children admitted to the Children's Hospital with pneumonia of obscure origin. Since, later, it became evident that only a few adenoviruses were found in this group, the study was extended to include cases with undifferentiated acute respiratory disease in the same hospital and a corresponding material in the Infectious Diseases Hospital.

In all the children stool specimens were examined for adenovirus at a very early stage of the infection. In a few cases nasopharyngeal secretion was also examined. Acute-phase and convalescent sera taken at

an interval of about 2 weeks were always asked for but were obtained in only 129 cases. Thus, the group-specific complement-fixation (C.F.) test against adenovirus was (simultaneously) performed on at least two serum samples only in these cases. The type-specific neutralization (N) test against AV7 was done in virus-positive cases only. Details concerning the virus isolation technique (roller tube cultures of human embryonic lung) and the methods of determination of C.F. and N antibodies were given in a previous report (15).

As controls were used 107 children (28 between 0 and 4, 47 between 5 and 9, 32 between 10 and 14 years old) admitted to the Infectious Diseases Hospital with aseptic meningitis in 1955-1956, who were examined for the presence of virus by the same technique as that used in the present study. Cases of parotitis and mononucleosis were excluded.

In most children naso-pharyngeal as well as nasal and pharyngeal swabs were taken and cultured for bacteria on admission or before antibiotic therapy was started. Insofar as the serum supply after the virological assay permitted, paired sera were simultaneously examined for antibodies to bacteria actually found in the cultures. The bacteria especially looked for in the cultures, the corresponding antibody reaction, and the conventional upper limits for their normal variation were as follows:

Pneumococci—antipneumolysin (APL) 500 (33)

β -haemolysing streptococci (streptococci)—antistreptolysin (AS) 200 (9, 12, 17, 36)

Pyogenic staphylococci (staphylococci)—antistaphylolysin (AStA) 1.4 (19, 36)

Haemophilus influenzae—complement-fixing antibodies to *H. influenzae* (AHI) 30 (32)

Escherichia coli (coli)—anticolilysin (ACol) 400 (37)

Epidemiological background

According to official records (20) influenza in epidemic form did not occur in Stockholm

TABLE 1. *Type distribution of virus strains isolated from 196 children with respiratory diseases. Frequency of significant rise ($> 4 \times$) in complement fixation (C.F.) test against adenovirus.*

Isolation from stools	Number of cases	Frequency of significant rise in C.F. test against adenovirus
Adenovirus		
Type 1	3	0/2 ^b
2	9	1/4
3	17	7/14
5	4 ^a	0/1
7	25	15/17
Other types	1	1/1
Poliovirus		
Type 3	1	0/1
ECHO-virus		
Type 9	1	0/1
Unidentified cytopathogenic agents	7	0/5
No virus recovered	129	7/83
Total	197	31/129

^a One of them was found to excrete Type 5 in the first specimen followed by Type 1, one and two weeks later.

^b Nominator: cases with significant rise. Denominator: tested cases.

during the time of investigation. The number of children hospitalized for primary atypical pneumonia increased considerably in the autumn of 1954 and of 1955 (26, 28), which was one reason why this study was undertaken. The incidence of poliomyelitis, another virus disease that may give catarrhal symptoms only, was low in 1954-1957. Aseptic meningitis associated with ECHO-virus Type 6 was prevalent in 1954-1955 (38). No epidemic of scarlet fever occurred during the period of investigation (20).

Results

Virological data

The number of children with acute respiratory disease in whom cytopathogenic

ie agents (adenovirus, poliovirus, ECHO-virus, and unidentified pathogens) were isolated, is seen in Table 1. The commonest types of adenovirus were 3 and 7. Their presence was also most frequently accompanied by significant increases in the titre of C.F. antibody to adenovirus. Such increases were also found in a few children without positive results for virus. Neither the child with poliomyelitis nor the one with ECHO-virus exhibited any clinical symptoms referable to the central nervous system, but merely catarrhal symptoms. Lumbar puncture was not performed, however.

From the 107 controls ECHO-virus was isolated in 17, poliovirus in 16, Coxsackie-virus in 1, unidentified agents (not adenovirus) in 21, and adenovirus (Type 7) in only 2. In 1 of the latter 2 the diagnosis of aseptic meningitis was questionable, since only 6 leucocytes per ml were present in an otherwise normal cerebrospinal fluid. In the other one there were 8 cells per ml, but the diagnosis was supported by a transient dysrhythmical electroencephalogram. Both children had clear signs of respiratory disease co-existing with the proven fresh infection with AV7. For the purely descriptive part of this study these two controls are included in the adenovirus group, whereas for the statistical analysis they are retained in the control group.

Infection with adenovirus Type 7

Only those 27 cases from which AV7 was isolated will be described here. The distribution by years of the isolations was as follows: for 3 months in 1954, 0 isolations; in 1955, 13; in 1956, 9; and for 8 months in 1957, 5 isolations. Virological data on these 27 children are set out in Table 2. Fifteen were patients at the Children's Hospital and 12 at the Infectious

TABLE 2. *Data on patients from whom adenovirus Type 7 was isolated.*

ND = not done; d = day after onset of illness.

Case no.	Age of patient (years)	Antibodies against adenovirus			
		Neutralizing (Type 7)		Complement-fixing	
		Serum 1	Serum 2	Serum 1	Serum 2
1	8	+++	+++	16 (4 d)	64 (10 d)
2	9	0	++	<2 (3 d)	64 (8 d)
3	8	0	+++	<2 (6 d)	16 (80 d)
4	10	0	++	<2 (2 d)	16 (16 d)
5	12	0	++	<2 (6 d)	64 (14 d)
6	9	0	++	<2 (7 d)	8 (20 d)
7	7	0	++	<2 (3 d)	256 (10 d)
8 ^a	8/12	0	+++	<2 (8 d)	32 (21 d)
9 ^a	11	+	+++	8 (7 d)	64 (17 d)
10 ^a	5	+	+++	8 (9 d?)	64 (19 d?)
11 ^a	8	0	++	4 (6 d)	32 (13 d)
12	1.5	+	+++	16 (7 d)	64 (12 d)
13	1.5	0	++	<2 (9 d)	32 (27 d)
14	1	ND	+	<2 (6 d)	16 (13 d)
15	5	+	++	32 (8 d)	64 (15 d)
16	7	(+)+	++	8 (2 d)	32 (16 d)
17	7/12	0	++	<2 (2 d)	8 (32 d)
18	6	ND	ND	<2 (4 d)	16 (13 d)
19	8	0	ND	4 (5 d)	ND
20	11	ND	ND	ND	ND
21	10	ND	ND	<2 (5 d)	ND
22	13	ND	ND	4 (11 d)	ND
23	8	ND	ND	ND	ND
24	1.5	++	++	64 (20 d?)	32 (26 d?)
25	3	ND	ND	>2 (5 d)	ND
26	1	ND	ND	ND	ND
27	1	ND	ND	ND	ND

^a Virological examination of nasopharyngeal secretion, which was done in these cases only, showed presence of adenovirus Type 7.

Diseases Hospital. In 18 of 19 serologically examined children (Cases 1-18) there was a significant (at least fourfold) titre increase in C.F. and/or N antibodies. Thus, the virus infection was well correlated in time to the respiratory disease. In the remaining 9 (Cases 19-27) adequate paired serum samples were not obtained and it cannot, therefore, be established whether or not the onset of the AV7 infection was correlated to the disease.

TABLE 3. *Bacteriological findings in 26 children in whom adenovirus Type 7 was isolated and bacterial culture was made.*

ND = not done. The serological tests are assessed only in those cases in which 2 paired sera were examined.

Bacteria	Number of isolations	Serological tests				
		AS	ASta	API	AHI	ACol
<i>No treatment before culture</i>						
Streptococci . . .	4	1 ^a + 0 ^b (2) ^c	0 + 2 (2)	0 + 1 (1)	0 + 1 (1)	0 + 1 (1)
Staphylococci . .	3	1 + 0 (1)	0 + 1 (2)	1 + 0 (1)	ND	ND
Pneumococci . . .	3	0 + 1 (1)	1 + 0 (1)	0 + 0 (1)	0 + 1 (1)	0 + 1 (1)
H. influenzae . . .	1	ND	ND	ND	ND	ND
No bacteria	5	1 + 1 (4)	1 + 2 (4)	0 + 2 (2)	0 + 2 (2)	0 + 0 (1)
<i>Treatment before culture</i>						
Staphylococci . . .	1	ND	ND	ND	ND	ND
Pneumococci . . .	1	ND	ND	ND	ND	ND
H. influenzae . . .	6	2 + 0 (3)	0 + 2 (2)	ND	0 + 3 (3)	0 + 1 (1)
No bacteria	6	0 + 2 (5)	1 + 2 (5)	1 + 2 (4)	0 + 4 (4)	0 + 3 (3)
Total	30	5 + 4 (16)	3 + 9 (16)	2 + 5 (9)	0 + 11 (11)	0 + 6 (7)

^a Serological response suggesting infection with bacteria.

^b Actual bacterial infection improbable.

^c Number of cases tested. See the text.

Bacteriological data

Twelve children were treated with chemotherapeutic and/or antibiotic agents prior to sampling for culture. In 6 of these *H. influenzae* was isolated, in 1 case together with staphylococci and in 1 case with pneumococci. In the remaining 6 the absence of pathogenic bacteria in the cultures does not rule out the presence of such organisms before treatment.

Among the 15 untreated children 9 had pathogenic bacteria, 2 of them two types, and in 1 child no cultures were made. In an attempt to evaluate the significance of the bacteriological findings these were compared with the serological results, as shown in Table 3. A reaction was considered as suggestive of an actual infection 1) when a titre increase was greater than

twofold (6 tests, in 2 of which it was \geq fourfold), 2) when a subsequent titre decrease of the same order of magnitude (4 tests) indicated that the first value, as a result of a possible actual infection, was likely to be above the ordinary level of the particular child. Two or more almost identical titres not exceeding the conventional limit for normal variation were considered as fairly contradictory to a fresh infection.

Epidemiological data

A remarkable fact was that no less than 26 of the 27 children in whom AV7 was isolated resided in the southern part of Stockholm, although at least the Infectious Diseases Hospital receives patients from the whole of Stockholm. It will be

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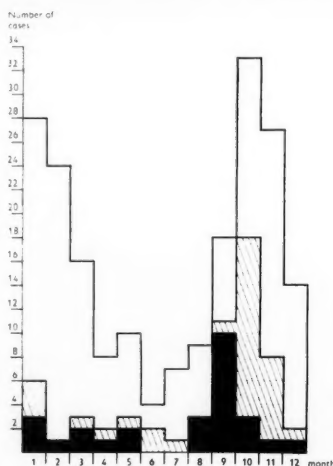


Fig. 1. Monthly incidence of acute respiratory infections in 198 children (including 2 cases with signs of concurrent aseptic meningitis and adenovirus Type 7 in their stools). Comparison between 27 children (■) with adenovirus Type 7, and 33 children (▨) with other types of adenovirus in their stools, and 138 children (□) in whom no adenovirus was found in the stools.

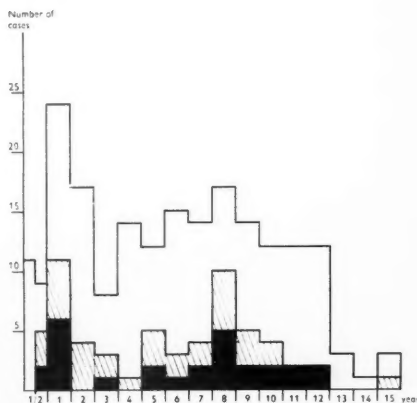


Fig. 2. Age-distribution of 198 children with acute respiratory infections (including 2 with signs of concurrent aseptic meningitis and adenovirus Type 7 in their stools). Comparison between 27 children (■) with adenovirus Type 7, and 33 children (▨) with other types of adenovirus in their stools, and 138 children (□) in whom no adenovirus was found in the stools.

seen in Fig. 1 that most of the children from whom adenovirus, including Type 7, was isolated became ill in the autumn. Fig. 2 shows the age distribution. In 15 cases in which AV7 was isolated no source of infection could be traced. Of 4 children 2 had possibly been in contact with each other at one school and two at another school. Four children belonged to the group of suspected nosocomial infections, though only 2 of them stayed in the same ward. One child could have contracted the infection during previous hospitalization, since she became ill with respiratory disease 5-6 days after discharge and had to be re-admitted (26). In a nursery where in 1956 adenovirus Types 1, 2, 3, and 5 were isolated (29) pneumonia developed, in 1957, simultaneously in 2 children in whom an AV7 was recovered. Finally, 3

siblings became ill within 7 days and were found to harbour AV7 and display significant titre increases by C.F. and/or N tests for this agent (27).

Clinical observations

As adenovirus may be excreted for a fairly long time after the onset of infection (15), the clinical study has been restricted to those 18 virus-positive children (Cases 1-18) in whom a titre increase indicated that a fresh AV7 infection co-existed with the respiratory disease. It will be seen in Fig. 3 that the clinical picture was dominated by fever, rhinitis, and pharyngitis, while cervical lymphadenitis and conjunctivitis were seldom seen, though they are common in adenovirus Type 3 infections. Occasionally the disease was manifested only by fever with slight objective

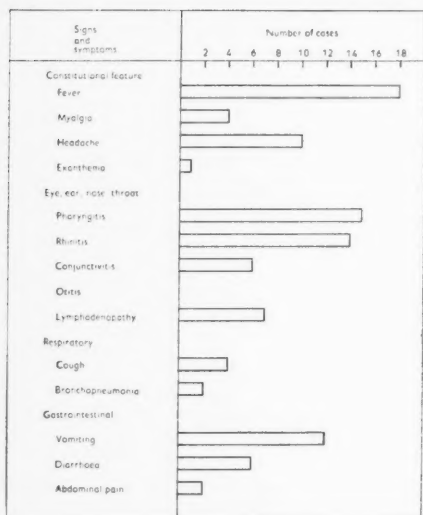


Fig. 3. Summary of the clinical features of 18 children with proven adenovirus infection Type 7.

symptoms referable to the respiratory tract.

The onset was often sudden, the temperature rising to 39–40°C in 1–2 days. The fever lasted for 5–12 days (mean 7 days) and ended in slightly more than half of the cases equally suddenly in 1–2 days. In some cases the temperature spiked on the last few days before it returned to normal. During the febrile stage many children had headache, muscle pain, and vertigo. Nausea and vomiting were common, and one-third of the children had loose stools, two of them abdominal pain as well. One child had on admission a slight non-characteristic exanthema. Conjunctivitis was generally bilateral and of moderate severity, except in 1 child who had an intense pseudomembranous inflammation with recovery of *H. influenzae* from the ocular discharge. The rhinitis

was usually attended by sparse discharge and was mostly manifested by nasal obstruction. The pharynx and the tonsils were in some cases quite pale, but in most cases slight or moderate inflammation was seen. Only 1 patient had marked changes in the tonsils with plugs, but no evidence of streptococcal infection. The lymph nodes were seldom markedly enlarged or tender, and were found in the neck and occasionally in the nucha.

The paranasal sinuses were examined by X-ray in 10 children, and in 4 of these the maxillary sinuses were found to be completely occluded, while in 2 there was only slight thickening of the mucosa. No less than 8 of 10 radiographically examined children had adenoid vegetations.

Rales were heard over the chest in only 3 children, of whom 2 (Cases 8 and 13) showed radiographic evidence of bronchopneumonia. In 10 others X-ray of the chest was normal.

The general condition of the children was good, excepting those 2 who had bronchopneumonia, who were critically ill.

Two children (Cases 4 and 7), as previously mentioned, had on admission slight pleocytosis (8 and 6 cells per ml, respectively, in an otherwise normal cerebrospinal fluid); 1 of them had also a transient pathological electroencephalogram. Both had evident signs of respiratory infection. In a further 4 lumbar puncture was performed and showed no abnormalities.

The erythrocyte sedimentation rate of the children, recorded by a micro-method, was between 17 and 54 mm in 1 hour. Measured by the ordinary method in the rest of the cases it varied from 8 to 36 mm in 1 hour. No anaemia was seen. The white-cell counts were between 2200 and

14,000, mostly in the range of 6000-8000, with a normal distribution or slight increase in neutrophils. The urine was normal.

It may be mentioned that the clinical picture in 5 of the children who were not fully investigated serologically was similar to that described above, with a basic syndrome of fever, pharyngitis and rhinitis. A further 3 children (Cases 24, 26, 27) had bronchopneumonia and purulent otitis. One child (Case 20) was treated for scarlet fever but had had respiratory infection about a fortnight before admission.

Finally, no signs of tuberculous disease were present in any of the children.

Discussion

The aetiological factors in respiratory tract infection are not easily established, which renders studies on the relationship between the aetiology and the clinical features, and the assessment of the therapeutic results difficult.

The isolation of a potentially pathogenic agent in an individual case does not by itself signify a causal relationship, particularly as two or more such agents are often recovered simultaneously. Pathogenic agents can also be harboured for a long time after the acute infection. On the other hand, negative bacterial cultures or negative results of virus isolations do not definitely rule out a bacterial or viral origin, since they may be ascribed to various disturbing factors, for instance faulty technique of sampling.

By the demonstration of a significant increase in an antibody to the isolated agent, the correlation in time between the infection and the disease can be established, though this is not equivalent

to a causal relationship. If no titre increase in antibodies to any other agent known to produce respiratory diseases are found, the aetiological significance of the isolated agent is further strengthened. However, simultaneous increases in the titre of antibodies to two or more agents are common. In this case it is impossible to judge which agent is primarily responsible for the disease, and a complex aetiology has to be accepted, unless the possibility of anamnestic reactions is taken into consideration. Moreover, no serological study can be complete, because there are sure to exist unknown agents which may produce diseases of the type observed. Finally, a wholly or almost wholly symptomless infection may be associated with very high antibody formation, while a severe infection may be accompanied by scarcely noticeable antibody response. The ability to form antibodies against different agents is also dependent on the child's age, the type of causal agent, and the site of infection (4, 5, 31, 32, 33, 34, 35). This applies especially to infection with *H. influenzae* (31).

The assessment of the aetiological significance of a demonstrated virus infection in individual cases of a certain illness (10, 11) must, however, be based on virological studies of epidemics of the illness, at which suitable controls are available for statistical analysis. By such a study (16) it has, for instance, been possible to demonstrate a significant relationship between adenovirus Type 3 infection and pharyngo-conjunctival fever.

Among our 196 children with different types of respiratory infection adenovirus was isolated in 58 (29.6%). By the demonstration of significant increases in the titre of

C.F. and/or N antibodies the correlation in time between the virus infection and the actual disease could be established in 25 of the 39 virus excretors examined. In a further 7 of 90 examined children significant titre increases were found, though no virus was isolated, as shown in Table 1. Thus, a fresh infection with adenovirus was demonstrated in 24.8% of 129 serologically investigated children with acute respiratory disease.

As regards AV7, 27 children were positive, including 2 with slight pleocytosis. In 18 of 19 serologically investigated children the correlation in time was shown by significant increases in antibody.

To ensure a truthful comparison of the incidence of AV7 between the respiratory-infection group and the controls, we excluded from the former group 31 children examined on account of direct suspicion of nosocomially contracted adenovirus infection, 3 who with respect to age, and 67 who with respect to the time of illness differed from the controls. The 2 children with aseptic meningitis were brought back to the control group. Of the remaining 95 with respiratory disease, 16 were positive for AV7, as against 2 of the 107 controls with aseptic meningitis. The difference, by the χ^2 test, is highly significant. The adequacy of the control material may be questioned, as the presence in this group of other viruses could have reduced the possibility of isolating AV7. The statistical proof of the correlation between AV7 isolated from the stools and acute respiratory disease in children has to be accepted with this reservation.

As a comment to the epidemiological data may be mentioned the absence of direct contact between several of the cases, among them most of the nosocomial ones. The explanation of this may be that in-

apparent cases have spread the infection, similarly to Barr's *et al.* (1) observation in a hospital outbreak of adenovirus Type 3 infections.

The question whether such symptomless AV7 infections occur in children, and if so, to what extent, cannot be answered here, since our material was selected solely on the basis of presenting symptoms referable to the respiratory tract. Thus, no investigation was made of environmental factors.

The bacteriological study of the 27 AV7-positive children, summarized in Table 3, showed that potentially pathogenic bacteria were present in 15, in spite of the fact that many of them had been treated with antibiotics before the swabs were taken. Further, bacterial infections are likely to be under-represented, since cases of promptly diagnosed bacterial origin may have been left out of the investigation, while those with poor response to antibiotic therapy were liable to be included.

An assessment according to the principles outlined above gave the following results: AS 5 positive reactions, 4 negative; AS_{St} 3 versus 9; API 2 versus 5; AHI 0 versus 11; ACol 0 versus 6, making 10 positive reactions in 9 children. On the other hand, all the five reactions were not negative in any patient, four were negative in 3, three were negative in 4, two were negative in 2, and one was negative in 7 cases. The proportions will stand out more clearly if expressed as follows: Of 59 serologically responses 10 were positive, 35 negative, and 14 uncertain. Thus, though far from complete, the sero-bacteriological investigation indicates that in some children a bacterial infection co-existed with

the virus infection. In others the occurrence of at least some of the commonest bacterial infections is rendered unlikely, and, hence, bacterial infection does not seem to be necessarily associated with the development of the described type of disease. That bacterial infection is common in association with many types of primarily virus diseases is well known.

Of the 9 children with positive serological response 7 belonged to the group of 18 with fresh AV7 infection. As an illustration may be mentioned Cases 2 and 8. The child in Case 2 had a significant streptococcal infection (fourfold increase in AS) and was quickly freed from bacteria by penicillin therapy but was not relieved from other symptoms of infection (the fever), a fact which suggests that these are dependent upon the simultaneously demonstrated virus infection. In Case 8 treatment with several antibiotics produced no clinical effect (26).

In conclusion, it seems probable that

AV7 may in children, too, give rise to marked febrile conditions with pharyngitis, rhinitis and occasionally atypical pneumonia, or in other words, clinical pictures resembling those described in adults with AV7 infections (3, 6, 25) and observed in English school-children by Tyrrell *et al.* (30) and Kendal *et al.* (13).

The clinical picture is, however, not sufficiently characteristic for an aetiological diagnosis to be based on it, as may be the case between pharyngo-conjunctival fever and adenovirus Type 3, and therefore, virological examination is necessary as a basis for the diagnosis.

Acknowledgement

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Summary

From the stools of 196 children with acute respiratory disease, examined during the period October 1954 to the middle of 1957, adenovirus Type 7 was isolated (1955-1957) in 25 cases. In a further 33 children the stools showed growth of adenovirus belonging to Types 1, 2, 3, and 5, and a strain not belonging to either of Types 1-7, 9 or 10. Adenovirus Type 7 was present in only 2 children among a number of cases of aseptic meningitis examined during 1955-1956. Both these children had, in addition, evident signs of infection of the respiratory tract. Significant increases in the titre of complement-fixing and/or neutralizing antibodies were found in 18 of 19 serologically examined children who had adenovirus Type 7 in their stools. The probable aetiological significance of adenovirus Type 7 infection to the symptoms of respiratory disease is discussed on the basis of the fact that potentially pathogenic bacteria were isolated from many Type 7 positive cases. In 9 such cases serological tests indicated a possible concurrent bacterial infection.

The most common symptoms in the children with a fresh adenovirus Type 7 infection (positive culture of faeces and serologically significant titre increase) were high fever of

relatively long duration, pharyngitis and rhinitis. Their general condition was good, except in 2 who had pneumonia with an atypical course, both of whom were critically ill. Most of the children examined by X-ray had sinusitis and adenoid vegetations.

It should be stressed that the clinical pictures observed in cases of adenovirus Type 7 infection are not sufficiently characteristic to allow any conclusions concerning the causative factor. The diagnosis of adenovirus Type 7 infection in children can, in the individual case, only be made probable by virological examinations.

Addendum: After this paper was completed, Chany et al. (France) in *Am. J. Hyg.* 67: 367, 1958 have described cases of AV7-infection in children with pneumonia, a few of which terminated in death.

Les infections à adénovirus du type 7 chez les enfants et leurs rapports avec les maladies respiratoires aiguës.

Sur 196 enfants atteints de maladie respiratoire aiguë qui ont été examinés au cours de la période s'étendant du mois d'octobre 1954 jusqu'à la moitié de 1957, il y en a eu 25 dans les selles desquels des adénovirus du type 7 ont été isolés. Les selles de 33 autres enfants renfermaient des adénovirus des types 1, 2, 3 et 5 ainsi qu'une souche n'appartenant à aucun des groupes 1 à 7, 9 ou 10. Dans un autre groupe d'enfants atteints de méningite aseptique qui furent examinés en 1955 et 1956, deux seulement présentaient des adénovirus du type 7. Ces deux enfants présentaient en outre des signes évidents d'une infection des voies respiratoires. Une augmentation significative du titre des anticorps de fixation et/ou de neutralisation du complément fut constatée chez 18 des 19 enfants dont les selles renfermaient des adénovirus du type 7 et qui furent soumis à un examen sérologique. La signification étiologique probable des infections à adénovirus du type 7 vis-à-vis des symptômes de maladie de l'appareil respiratoire est discutée sur la base du fait que des bactéries potentiellement pathogènes ont été isolées dans de nombreux cas où la recherche des adénovirus du type 7 avait été positive. Dans 9 de ces cas, les résultats des tests sérologiques indiquèrent la possibilité d'une infection bactérienne concurrente. Les symptômes les plus fréquemment observés chez les enfants victimes d'une infection récente à adénovirus du type 7 furent de fortes poussées de température d'une durée relativement longue, des pharyngites et des rhinites. L'état général de ces petits malades était bon, sauf chez deux d'entre eux qui étaient atteints de pneumonies à évolution atypique et qui furent chacun sérieusement malades. La plupart des enfants qui firent l'objet d'un examen radiographique étaient affligés de sinusite et de végétations adénoïdes. Il y a lieu de souligner que la symptomatologie clinique observée dans les cas d'infections à adénovirus du type 7 n'est pas suffisamment caractéristique pour que l'on puisse tirer des conclusions quelconques au sujet de l'agent causal. Le diagnostic d'une infection à adénovirus du type 7 chez les enfants peut simplement, dans chaque cas, être rendu probable par des examens virologiques.

Infektion mit Adenovirus Typus 7 bei Kindern und ihre Beziehung zur akuten Erkrankung der Atemwege.

Aus den Stühlen von 196 Kindern mit akuter Erkrankung der Atemwege in der Zeit von Oktober 1954 bis zur Mitte 1957 wurde Adenovirus Typus 7 von 25 Kindern isoliert. Bei weiteren 33 Kindern wurden Adenoviren der Typen 1, 2, 3 und 5 und ein weder zum Typus 1-7, 9 oder 10 gehöriger Virusstamm aus den Stühlen kultiviert. Adenovirus Typus 7 fand sich nur bei 2 Kindern unter einer Anzahl von Fällen von aseptischer Meningitis, welche in den Jahren 1955-56 untersucht wurden. Von Beiden Kinder wiesen überdies klare Anzeichen von Infektion der Atemwege auf. Ein signifikanter Anstieg im Titer der komplementbindenden und/oder neutralisierenden Antikörper wurde bei 18 unter 19 serologisch untersuchten Kindern, welche Adenovirus Typus 7 im Stuhl enthielten, gefunden. Die Wahrscheinlichkeit einer ursächlichen Bedeutung der Infektion mit Adenovirus Typus 7 für die Symptomatologie der Erkrankung der Atemwege wird unter Berücksichtigung der Tatsache, dass bei vielen Fällen mit positivem Adenovirus Typus 7 Befund potenziell pathogene Bakterien isoliert worden waren, erörtert. Bei 9 solchen Fällen wiesen serologische Untersuchungen auf eine möglicherweise gleichzeitig ablaufende bakterielle Infektion hin. Die häufigsten Symptome bei Kin-

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dem mit frischer Infektion mit Adenovirus Typus 7 waren hohes, relativ langanhaltendes Fieber, Pharyngitis und Rhinitis. Ihr Allgemeinzustand war gut, ausser bei zweien, die atypisch verlaufende Pneumonie hatten und deren Zustand als kritisch bezeichnet werden musste. Die Mehrzahl der Kinder, die röntgenologisch untersucht wurden, hatte Sinusitis und adenoide Vegetationen. Es muss unterstrichen werden, dass die klinischen Bilder, welche bei Krankenfällen mit Infektion mit Adenovirus Typus 7 beobachtet werden, nicht genügend charakteristisch sind, um sichere, den kausalen Faktor betreffende Schlussfolgerungen zuzulassen. Die Diagnose einer Infektion mit Adenovirus Typus 7 bei Kindern kann im individuellen Fall auf Grund einer virologischen Untersuchung nur als wahrscheinlich gestellt werden.

Las infecciones con Adenovirus Tipo 7 en niños y su vinculación con las enfermedades respiratorias agudas.

El Adenovirus tipo 7 fué aislado 25 veces en las deposiciones de 196 niños con enfermedades respiratorias agudas, examinadas durante el período comprendido entre Octubre de 1954 y mediados de 1957. En otros 33 niños las deposiciones mostraron un crecimiento de Adenovirus pertenecientes a los tipos 1, 2, 3 y 5 y una cepa no perteneciente a los tipos del 1 al 7, ni tampoco al 9 o 10. Adenovirus Tipo 7 se halló presente en solamente 2 niños entre un número de casos de meningitis aséptica examinados en 1955-1956. Ambos niños tenían, además, signos evidentes de infección en el tracto respiratorio. Fué hallado un significativo aumento en el título de anticuerpos neutralizadores, y/o fijadores del complemento en 18 de los 19 niños examinados serológicamente entre los que presentaban Adenovirus Tipo 7 en sus materias fecales. El probable significado etiológico de la infección por Adenovirus Tipo 7 en los síntomas de la enfermedad respiratoria es discutido, partiendo del hecho de que bacterias potencialmente patógenas fueron aisladas en muchos casos Tipo 7 positivos. En 9 de dichos casos los test serológicos indicaron la posible concurrencia de una infección microbiana. Los síntomas más comunes en los niños con infección a Adenovirus Tipo 7 en actividad, fueron fiebre elevada de relativamente larga duración, faringitis y rinitis. Su estado general fué bueno, con excepción de 2 que presentaron una neumonía de evolución atípica, en ambos muy grave. La mayoría de los niños examinados radiológicamente tenía sinusitis y vegetaciones adenoideas. Debe destacarse que los cuadros clínicos observados en los casos de infección a Adenovirus Tipo 7, no son los suficientemente característicos como para permitir extraer conclusiones con respecto al factor causal. El diagnóstico de la infección por Adenovirus Tipo 7 en los niños, puede, en los casos individuales, ser sólo de probabilidad por el examen virológico.

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The Children's Hospital "Samariten"
Ringvägen 21
Stockholm Sö.
Sweden

PROCEEDINGS OF PEDIATRIC SOCIETIES

Danish Paediatric Society

Meeting October 22, 1958

Knud Bojlén: Investigation of the incidence of tuberculosis in a school

(To be published in Ugeskr. læger.)

DISCUSSION: *P. Drucker* has investigated the reliability of tuberculin reactions carried out by the Mantoux test with 5 tuberculin units (T.U.) and found that a number of school children who previously reacted positively now reacted negatively. It was shown by the Moro plaster test that 26 out of 30 children were Moro positive. Later, 29 school children who had previously reacted positively were found to react negatively to the new Mantoux with 1 T.U. Employing the Mantoux with 10 T.U., 23 of these children reacted positively. Dr. D. is, therefore, of the opinion that the question of the potency of the tuberculin employed should once more be reviewed to avoid unnecessary BCG revaccination. — *Ole Christensen* demonstrated previously that very potent sources of infection are still discovered in Copenhagen, particularly among elderly men living alone and that tuberculosis in children has diminished much less in pre-school children than in school children since BCG vaccination became available to all school children (from 1948). Three to five per cent of children in Copenhagen have already been infected with virulent tubercle bacilli at the commencement of school age while for example in Stockholm one per cent positive spontaneous reactors are found in the same age group. Dr. C., therefore, sup-

ported the recommendation that BCG vaccination be carried out during the first year of life to a much greater extent than previously. — *K. Rasmussen* could not wholeheartedly support the idea of ceasing BCG vaccination in the provinces, particularly when the ever present possibilities of contact with more infectious localities are considered, e.g. by means of the increasing connections with other countries. — *Esther Ammundsen* remarked in connection with the relatively high percentage of positive reactors in the first classes that it should be borne in mind that regular mass investigation for tuberculosis is only undertaken on approximately 250,000 of the 750,000 inhabitants of Copenhagen, viz. the population employed outside their homes. The extent of the risk of infection in the groups of the population not hitherto examined regularly, particularly in women working at home and elderly individuals will now be investigated in one of the Central Tuberculosis Dispensaries in connection with a spot check examination of approximately 1000 selected individuals in the municipality of Copenhagen. The result of this investigation will play a part in the determination of the policy to be followed in future.

P. Plum and W. Trojaborg: Some cases of hypersarrhythmia ("Salaam spasms")

Sorel & Dusaucy Bauloye stated in 1958 that a number of cases of salaam spasms may be treated with ACTH with subsequent

normalization of the electroencephalogram and cessation of the seizures. In the Paediatric Clinic, the University Hospital, Copenhagen, a clinical trial is at present being carried out to investigate this claim. Eight children showing this clinical picture and varying in age from four months to three years were tested from July to October 1958. As a rule, 10 units of Acton prolongatum were administered daily for two to six weeks. Two of the children became free from seizures, two improved while the incidence of seizures remained unchanged in the other cases. It is still too early to express any opinion regarding any improvement in the mental condition of the children. The EEG became normalized in one of the two children who became free from seizures while in two other cases it became less abnormal. In the remaining cases, no change was observed in the EEG.

The seizures were relatively uniform in nature in the cases in this material and consisted of a series of isolated contractions or spasms involving the head, trunk, arms and legs frequently so that the head and trunk were bent forwards and the arms and legs flexed. The individual contractions are extremely rapid while the intervals may be from 10 to 30 seconds, i.e. longer than in clonic seizures. The number of contractions per series varies from 10 to 70. The majority of children in this material showed signs of severe cerebral lesions and the prognosis as regards the intellectual development is poor.

P. Thygesen and Chr. Hansted: Hypsarrhythmia

A case of typical hypsarrhythmia is recorded. The patient was a girl aged five months who had previously been healthy and had developed completely normally. The infant took ill suddenly with rapidly progressive attacks of spasms associated with increasing lassitude, inactivity and apathy. The condition remained uninfluenced by anti-epileptic drugs but after treatment with ACTH for 10 days with continued dimedione therapy, the child

rapidly became free from seizures and became active and interested while the EEG changes simultaneously disappeared practically completely. Two and a half months later, the patient is still free from seizures and the development is normal.

DISCUSSION: *Sv. Brandt* does not consider that the condition is an etiological entity even although the fact that it appears suddenly at the age of 4-5 months in children who have previously developed normally has made this presumption tempting. Dr. B. has observed 17 children with hypsarrhythmia in the EEG Out-Patient Department, Queen Louise's Hospital for Children, Copenhagen. Out of these, two had presented definite symptoms from the central nervous system after birth, one had epileptic seizures with normal EEG three months prior to the development of hypsarrhythmia at the age of seven months. Further, phenylpyruvic oligophrenia was found in one child, probable toxoplasmosis in another and probable kernicterus in a third. Three out of the 17 children died, all in states of dementia, five of the others were markedly demented and three were slightly sub-normal while the remainder were either too small for evaluation or were not followed up. The effect of treatment with ACTH was tried in two children. In one case no effect was observed while in the other the EEG became less abnormal but the clinical condition remained unchanged. If Sorel's report of the favourable effect of ACTH treatment with early institution of therapy holds true, all children exhibiting lesser motoric seizures commencing at about the age of five months must be hospitalized immediately. — *P. Thygesen* stressed that emphasis should be placed upon the very early manifestations of this form of epilepsy (which may be evidence of a constitutional factor of considerable significance) and upon the feature that the dysrhythmia and the clinical features of the seizures, as a rule, "burn out" prior to the age of 1-2 years and the surviving children are left with marked dementia. Such a course may be evidence of a type of im-

munebiological reaction in the central nervous system, perhaps related to the leucoencephalopathies and, similarly, the apparently dramatic effect of early ACTH therapy may be evidence of a process which is initially "functional" and reversible.

Henning Andersen: Mucus obstruction of the biliary tract

A boy aged two months was admitted to Queen Louise's Hospital for Children on account of severe jaundice, acholic faeces, bile pigmented urine and enlargement of the liver which developed a few weeks after birth. The child was poorly nourished, the serum bilirubin was found to be 27 mg% and cholecystography showed no secretion. As the symptoms did not develop until some time after birth, the possibility of a mucus biliary obstruction was considered and 5 ml 20 per cent magnesium sulphate solution was administered via a duodenal tube. The following day the faeces were distinctly pigmented with bile. As it could not be ascertained that the condition had been completely corrected, an explorative laparotomy was undertaken. The biliary tract was found to be of normal appearance and cholangiography via a tube inserted showed a normal biliary tree with free drainage into the duodenum. The subsequent course was uncomplicated and two months later the icterus had disappeared and the liver had practically returned to the normal size. At the age of 2½ years the child is well and thriving. The liver, liver function tests and cholecystography are normal.

A second child was admitted at the age

of 1½ months with symptoms resembling those in the first case but which had commenced at birth. The liver was enlarged, cholecystography showed no excretion and the faeces were acholic. Following administration of magnesium sulphate by a duodenal tube, faeces pigmented with bile were passed in the course of the next 24 hours and the condition improved rapidly. On follow-up examination at the age of one year the child appeared to be normal.

The clinical picture resembles that of the congenital atresia of the biliary tract but in certain cases a preliminary "free interval" or the intermittent presence of bile in the intestine may suggest the diagnosis. The cause of the condition is unknown. Congenital strictures in the biliary tract are supposed, under certain conditions e.g. dehydration, to be responsible for biliary obstruction. During recent years there has been a tendency to regard neonatal hepatitis as one of the main causes of the obstruction (Hsia). Some authors consider that treatment with magnesium sulphate is counterindicated on account of the toxicity. Dr. A. observed no side-effects. Bile acids (Decholin) administered intravenously together with their salts (Ketochol) orally are recommended by some as the best therapy.

DISCUSSION: It was mentioned in the discussion that even severely jaundiced children with mucus obstruction do not necessarily develop neurological symptoms but approximately ⅓ to ⅔ develop cirrhosis. Late jaundice is not necessarily synonymous with mucus biliary obstruction as it may also be observed in cases of aplasia.

Meeting November 20, 1958

P. Hertz: Accounts from the time of the inauguration of the Danish Paediatric Society

(Published in Ugeskr. læger 1959: 121: 23.)

The meeting was held to celebrate the

fiftieth anniversary of the Society. The Senior Physicians Dr. K. Krabbe, M.D., and Dr. C. Friderichsen, M.D., were elected as honorary members.

Meeting December 3, 1958

J. Lenstrup: Demonstration of two patients with autism

Henning Andersen: Sympathicoblastoma treated with vitamin B₁₂

In 1957 Bodian & White reported the results of treatment of neuroblastomata with massive doses of vitamin B₁₂. In a group of 29 children in all age groups regression was observed in 50 per cent while 25 per cent were apparently healthy after periods of observation of 1½-6 years. The latest British experience, hitherto unpublished, is even more encouraging. As the treatment is without side-reactions and as the results obtained are comparable with the results hitherto obtained following operation and/or radiation which are frequently associated with serious trauma, the decision was taken to employ the treatment on a boy aged eight months admitted to Queen Louise's Hospital for Children with a large tumour in the left lumbar region displacing the left kidney upwards and laterally and causing scoliosis. Rapidly increasing paralysis of both lower limbs and the bladder had occurred. There were no demonstrable metastases. At operation, a tumour was encountered deep to the left psoas muscle infiltrating nerves and muscles. The tumour was regarded as inoperable. Macroscopically, the tumour tissue resembled a sarcoma. Microscopical diagnosis: Malignant tumour, sympathicoblastoma/gonioma. Treatment with vitamin B₁₂ was commenced with 1 mg Cy-cobemin (NFN) intramuscularly daily and, after the elapse of a couple of weeks, the paralyses began to regress and the general condition improved. Ten months later, the tumour could no longer be palpated nor be seen in the X-ray. The left kidney had resumed its normal position. The paralysis of the bladder had disappeared completely and the boy was able to walk about freely but did not move the right foot quite normally. The scoliosis had disappeared. The treatment is still continued twice weekly. The child is growing and thriving normally and the results of blood examinations are

normal. It is, however, probably too early to make any statement regarding the prognosis.

According to British experience, the incidence of "spontaneous" recovery in extensive material of children is about one per cent. Isolated cases have been reported, particularly in children under one year of age in whom biopsy alone has been followed by recovery. These observations make evaluation of all therapy difficult. Until further experience is available, it appears justified to employ vitamin B₁₂ therapy parallel to or together with the forms of treatment hitherto employed.

DISCUSSION: *J. Vesterdal* had treated two patients according to the same principles. Both had metastases at the commencement of the therapy and both had died.

C. C. Winkel Smith and Preben Plum: Some cases of masculine pseudohermaphroditism

(To be published in Ugeskr. læger.)

In connection with the demonstration of four cases of masculine pseudohermaphroditism varying in age from early infancy to puberty, all of whom were chromatin negative and with testes, an account was given both for the diagnostic and therapeutic problems in these patients. The clinical investigation comprized cystoscopy, urethrography, hormone investigation, chromatin determination and possibly gonad biopsy and exploratory laparotomy. The group of masculine pseudohermaphroditism was demonstrated to consist of a very heterogenous collection of patients varying from markedly feminine individuals with completely female external genitalia (one of the four patients), various intermediate stages in which increasing virilizing may develop at puberty (two patients), possibly both with greatly increased androgens and oestrogens and, finally, the cases of vulvar hypospadias which are actually completely virile patients

despite the fact that the internal genitalia may be very undifferentiated and include both vagina and uterus. Treatment of these patients, as a rule, should not be considered until the commencement of puberty where the choice of treatment must depend upon a series of factors such as the external genitalia, hormonal constitution and, most important, the psychic pattern of the patients. Changes in the sex are probably not to be recommended after the first years of life have elapsed. In cases which resemble more or less conditions of intersex in which a mixture of virilizing and feminizing are present, castration must be considered. In the material presented here this was undertaken in two cases with subsequent hormonal therapy.

DISCUSSION: *Henning Andersen* did not consider that too much stress should be placed upon chromatin determinations alone. Dr. A. enquired whether mixed tumours should not be removed on account of the risk of malignant degeneration and whether the gonads should not be removed in children with feminine external genitalia but with large clitoris in order to avoid masculinization. — *C. C. Winkel Smith*: Chromatin determinations comprize only part of the total pattern but one sex must be chosen and it is undoubtedly easier for individuals who deviate from the normal to live as women than as men. Dr. W. S. had found that seven out of 79 mixed tumours became malignant.

Mogens Hansen: Arthrogryposis multiplex congenita

Forty cases of arthrogryposis multiplex congenita were collected from the Orthopaedic Hospital, Copenhagen, and of these 34 were followed up. During recent years, a

number of patients were treated according to new principles according to which attempts are made to improve the position of the joints and increase their function by means of soft tissue operation at as early a stage as possible. Attempts are made to conserve the majority of the normal structures and thus tendon lengthening operations were undertaken in preference to tenotomies and boney interventions were avoided. Interventions were undertaken upon the feet, knees, hips, hands and elbows. In several cases apparently useless muscles could be trained to a certain function following removal of the contractures and tendon lengthening. In all cases improvement of the position of the joints was obtained.

J. Balslev Jørgensen, E. Paridon and F. Quaade. The external volume of the cranium in normal, macro- and microcephalic children

(To be published in *Acta pædiat.* 48, 1959.)

DISCUSSION: *E. Busch* enquired whether the measurements undertaken were connected with the information obtained by X-ray examination of the cranium. Can variations in the circumference of the cranium be followed by this method? What changes in the external volume of the cranium are produced e.g. by a change of one cm in the circumference of the head? — *Chr. Hansen* did not consider that the weight was good as a correlation particularly in cases of hydrocephalus. — *F. Quaade* had not compared the measurements undertaken with measurements of the circumference of the cranium. The weight was perhaps not the best correlator, the length of the child from external auditory meatus to the soles of the feet might conceivably be employed instead as the height also changes in hydrocephalus.

Meeting January 14, 1959

Else Mortensen, Erik Hansen and Kjeld Nielsen: The incidence of pathological B. coli infections in paediatric wards

Else Mortensen: During the four-year period 1955-58, 62 cases of pathogenic *B. coli* intestinal infections were demonstrated in the Department of Paediatrics, Blegdam Hospital, Copenhagen. The infecting agent consisted of *B. coli* Types 26, 55, 111, 127. Only five cases occurred during the years 1955-56 but 31 in 1957 and 26 in 1958. Specimens of faeces were sent for bacteriological investigation from all suspected cases and during three periods of 3-4 weeks duration from all infants. Only one symptomfree bacterial carrier was demonstrated. In 1957 *B. coli* of Types 26 and 55 were encountered while Type 111 comprises 54 per cent of the cases in 1958. Both in 1957 and 1958 the fewest cases were demonstrated during the six winter months but there was no actual seasonal peak. The vast majority of the patients were less than six months of age and most of these were 1-2 months of age. The most severe cases occurred in the youngest age group. Twenty-five per cent of all the cases must be termed toxic. Types 26 and 55 occurred in the great majority of the most severe cases while Type 111 in the cases recorded produced slighter symptoms. The various types were equally distributed in all the age groups. Pathological stools were the most frequent symptom (84 per cent), vomiting occurred in 45 per cent and marked irritability in 35 per cent, practically exclusively in infants with *B. coli* Type 111. An attempt to elucidate the epidemiological conditions revealed that the infection was most frequently introduced by a child from an institution and this was followed by a series of nosocomial cases concentrated in an isolated building and within this in an isolated section and, for this reason, the possibility of air-borne infection was considered favoured by unfortunate conditions in the ventilation of the wards and sluice room.

Treatment: 20 cases were treated with chloromycetin and 32 with neomycin and ftyalsept. The latter therapy appeared to have a slightly more rapid effect, the criterion employed being three negative faecal cultures taken on three successive days. Four cases which were treated with penicillin and duostreptomycin, two cases treated with sulfacombin and duostreptomycin and three cases which were not treated became free from bacteria equally rapidly (approximately one week) all without recurrence. Recurrence took place otherwise in four and six cases, respectively. Thirteen further cases in the two treatment groups mentioned first showed at least three negative cultures before treatment was commenced as repeated attempts were made to clean the Department by simultaneous treatment of all the patients. It is, therefore, considered that treatment of these slight cases is of doubtful value if effective isolation can be attained. On the other hand, however, treatment can scarcely be withheld as long as the nosocomial infection implies a genuine risk for other children. In this material, five out of the 16 toxic cases were infected nosocomially.

Erik Hansen: In the Department of Paediatrics, Sundby Hospital, Copenhagen, an increase in the incidence of patients with dyspepsia and *B. coli* in the stools has apparently occurred in 1958 compared with the years 1955-57. The increase is, however, scarcely genuine as a nosocomial epidemic of *B. coli* Type 111 occurred in spring 1958. Comparison between the cases of dyspepsia in which so-called pathogenic *B. coli* appeared in the faeces and cases of dyspepsia in which no such bacteria were found showed that the coli dyspepsia occurs electively during the first three months of life, i.e. on the average earlier than cases of dyspepsia without growth of pathogenic strains of *B. coli*. Both forms of dyspepsia are more frequent among artificially fed infants than among breast-fed babies. The duration of the illness was uniform in the

two groups but the stools in the coli group took, on an average, slightly longer to return to normal than in the other group. Clinically, the coli dyspepsia in the period in question appeared to be slightly milder than the dyspepsia without *B. coli* in the faeces. The incidence of recurrence was found to be equal in the two groups. Practically all the cases of coli dyspepsia were treated with terramycin with good effect as judged from the clinical viewpoint and the disappearance of coli bacteria from the faeces but no control material is available in which treatment with antibiotics was not employed.

Kjeld Nielsen: In the Children's Hospital, Fuglebakken, 37 cases of coli enteritis were demonstrated during 1957 and 1958. Twenty-six of these cases occurred in six lesser epidemics in which a source of infection could be demonstrated and its nosocomial contact cases examined. Eleven cases were admitted with coli enteritis and demonstration of the infection to other cases in the Department could not be shown. Eleven cases were untreated apart from dietetic measures and all eleven were clinically normal on discharge but in only eight of these negative cultures had been obtained prior to discharge. Three of the patients were discharged for various reasons before control culture had been undertaken. Seven patients were very toxic and were treated with intravenous infusion and all received terramycin or neomycin-falysept. Sixteen other patients received terramycin and all showed negative cultures one week after the cessation of treatment. On account of the risk of the development of resistant staphylococci by the use of broad-spectrum antibiotics treatment with neomycin-falysept was later substituted in the Department. The eleven cases treated in this manner all showed negative cultures one week after the cessation of treatment. Otherwise, attempts were made to isolate the affected patients as far as possible.

DISCUSSION: *Oluf Andersen* had the impression that coli infections were not as dangerous as those observed during World War II but such infection is still dangerous

for debilitated children. Infected children should be isolated but there were, nevertheless, great possibilities for infection. Dr. A. did not favour treatment with the broad-spectrum antibiotics. Perhaps an attempt should be made with readily and less readily soluble sulphonamides. — *A. Dupont* considered it remarkable that infection with *B. coli* Type 111 had now assumed a milder course while previously it was the most dangerous. The question arises whether the infections mentioned by the introductory speakers were not due to types with another H-antigen than those which previously produced the severe infections. — *Früz Ørskov* emphasized the significance of complete bacteriological type determinations. The previously toxic *B. coli* 111 was 0111:B4:H2, but other strains of the same type exist but with another H-antigen. It has not been demonstrated that these other types have any relation to enteritis in infancy. — *Folke Tudvad* considered it would be of value if the paediatric departments could obtain complete bacteriological type determinations. Experience from Sundby Hospital suggests that a series of infants have *B. coli* in the faeces but the clinical course does not differ from cases of dyspepsia in which *B. coli* cannot be demonstrated in the faeces. This would help clinicians to obtain information regarding the extent to which the strain of *B. coli* concerned must be regarded as toxic. Dr. T. drew attention to the fact that in an apparently harmless epidemic one very toxic patient might occur. — *E. Flensborg* emphasized that it did not suffice only to treat the toxic patients as many of those infected nosocomially become very ill. Dr. F. did not consider that any of the treatments recorded hitherto were correct. He stressed the difficulty in isolating these patients. — *A. Dupont* in reply to *P. Plum:* In isolated cases a weakly increasing Widal reaction was found. — *P. W. Bræstrup* was of the opinion that a number of the cases of dyspepsia in which *B. coli* could not be demonstrated in the faeces were perhaps due to unknown strains. Air-borne infection is probably of great significance for the spread

of infection and for this reason positive pressure in the wards was to be recommended. Experience in the County Hospital in Gentofte demonstrated that thorough washing of the hands, washing door handles etc. could limit spread of infection. — *Sv. Tulinius* reported that an increase had occurred in the total number of *B. coli* infections demonstrated in the National Serum Institute on samples of faeces submitted from 170 in 1956 to 313 in 1958. The majority of cases originated from greater Copenhagen. There is no doubt that infections with *B. coli* are predominantly contact infections and that *B. coli* thrives well in the cool moist sluice rooms. It might be interesting to investigate the faeces or anal swabs from all infants e.g. under the age of one year who were hospitalized and the finer serology should be carried out in all cases.

Svein Vestermærk: Wissler-Fanconi's syndrome

A boy aged 11 years had spent a total of 1072 days in hospital in the course of the

past 7½ years on account of intermittent pyrexia, fleeting pain and swelling of the joints and transient non-characteristic episodes of exanthema. No chronic changes were present in the heart nor in the joints. This was probably a case of Wissler-Fanconi's Syndrome.

DISCUSSION: *Oluf Andersen* found it difficult to diagnose many of the joint conditions which are hospitalized particularly those which do not present the symptoms characteristic of rheumatic fever. Some of these cases are undoubtedly due to staphylococcal infections. Dr. A. had the impression that rheumatic fever and chorea had diminished in severity and that cardiac complications are more rarely observed in these diseases. Perhaps both of these diseases represent a collection of different conditions. — *Bent Friis-Hansen*: Wallgren has drawn attention to the alteration in the severity of cases of rheumatic fever. This alteration has occurred gradually and commenced prior to the era of antibiotic and hormone therapy.

F. Tudvad, Copenhagen.

Swedish Pediatric Society

Meeting February 13, 1959

C. Thorén and G. Sterky: Some rarely observed findings in juvenile hypothyroidism

The onset of juvenile hypothyroidism is often insidious and its diagnosis difficult. Anemia and obstipation are the usual erroneous diagnoses. It is not widely known that a high SR occasionally is associated with hypothyroidism and may be of great differential diagnostic significance.

A 13 year old girl, who for months was under control on account of a SR measuring approximately 50 mm, also was found to have a high AST, 3200 I.U., an increased ASTa, 5.6 I.U. Chills and fever supervened.

The SR rose to 120 mm. When X-ray disclosed a general cardiac enlargement, 435 cc/m², and the EKG presented isoelectric T waves, carditis was suspected, but the course was uncharacteristic. First a year later a myxedema was disclosed. Cholesterol 750 mg%. BMR minus 29%. SR became slowly normalized during treatment with thyroid extracts.

Packalén demonstrated in 1948 that AST could be unspecifically increased in hypercholesterolemia. The case under discussion presented both a specific and an unspecific titer enhancement. Inverted T waves in the EKG are much commoner than general low

voltage. Among 19 cases of hypothyroidism hospitalized during the last ten years, 6 presented pathological T waves while 2 showed only low voltage. A heretofore unmentioned phenomenon could be observed during work, when the T waves in the myxedematous girl became normalized. The pulse rate during work could not be pressed beyond 156 beats/min. Blood volume and total hemoglobin as well as oxygen saturation and respiratory quotient were low. Lactic acid production during work as well as the mechanical efficiency were normal. Beside the above mentioned findings, the girl had an enormously dilated colon which strangely enough caused her no discomfort. The megacolon picture disappeared during treatment with thyroid extracts. Finally a kidney stone was detected in the girl.

Another 13 year old girl with SR about 40 mm and an iron-resisting sideropenic anemia, who ceased to grow and lost 10 kg, was diagnosed as a moderately severe case of hypothyroidism. The same diagnosis was made in a 12 year old girl with cretinism. Her SR measured 45 mm. Among the 19 above mentioned cases, 10 presented SR higher than 20 mm, which demonstrates the frequency of this symptom. The latter girl had another interesting finding. X-rays revealed a definite epiphyseal dysgenesis in the femur, and this became normalized following treatment with thyroid extracts.

DISCUSSION.—*M. d'Avignon:* Touches upon a rarely observed finding in hypothyroidism, especially the infantile forms. Several cases were presented (personally communicated by Ph. Evans and his own) of patients with dysgenesis in the lumbar vertebral body which predisposes to kyphosis. The skeletal changes regressed following treatment with thyroid extracts. — *G. Sterky* in answer to a question posed by Dr. G. BERGLUND: No gamma-globulin increments were detected in the 3 presented cases which disclosed SR varying between 40 and 50 mm. However, α_2 and β fractions were slightly increased, as is usually observed in hypothyroidism.

L. Gardeström, B. Karlsson and B. Nau-mann: Physical treatment results in cerebral palsy

A modern cerebral palsy program has been conducted in the Kronprinsessan Lovisa's Barnsjukhus since 1951. The therapeutic results in 114 cerebral palsy cases have been examined according to the precise definitions formulated by the American Academy of Cerebral Palsy. The selected patients have undergone treatment for at least 3 years. During this time the physical treatment has mainly consisted of invalid gymnastics and no orthopedic-surgical treatment. The functional capacity has been graded on the basis of a 5-degreed scale: very slight, slight, moderate, heavy and very heavy capacity restriction. Following this scale, 53 patients improved 1 step and 9 patients 2 steps. Twenty-five of the 114 patients received inadequate treatment. Fifty-three of the 89 adequately treated patients (60 %) showed improvement while only 9 (36 %) of the 25 inadequately treated patients became better. The intensity of the treatment appears to be significant especially for hemiplegias and paraplegias. Athetoses and ataxias apparently improved irrespective of the intensity of treatment. The study would seem to stress the importance of commencing treatment as early as possible. Convulsive children and intellectually markedly retarded children appear to be less amenable to treatment. If one excepts tetraplegias, the normally talented, adequately treated patients comprise an *élite* group in which one observes the greatest number of improvements. This group comprised 45 patients of which 37 (82 %) became better.

DISCUSSION.—*M. d'Avignon:* This follow-up study fulfils a long-felt want; no earlier Swedish attempt to set forth the therapeutic results is available. Despite that some spontaneous improvements certainly are included in the follow-up findings of the physically treated patients, the results are most encouraging and should spur us on to still greater efforts. One factor which has been mentioned deserves further emphasis: com-

mencing the intensive treatment as early as possible. Such intensive physical treatment is indicated already at 1-2 years of age for periods of 2-3 months per year. Such an all-round treatment cannot be administered as intensively and efficiently at the patient's home as in an institution especially equipped for the proper treatment of such children. It is important, however, that the parents should be allowed to follow the treatment for a few days before the patient is discharged from the hospital. At this time they should receive instruction from the whole team of personnel having had charge of the patient's treatment: pediatricians, child psychiatrist, orthopedist, phoniatrician, physical therapist, Kindergarten-teacher, speech therapist, eventually auditory-training teacher and other nursing personnel. The training should be pursued at home following stated instructions, under the control of the local physical therapist.

G. Ekström: Rupture of pancreas with pseudo-cysts

G. Sterky and A. Thilén: Acute hemorrhagic purpura (Schönlein-Henoch's syndrome)

A preliminary report is given of a hitherto 80 % followed-up material comprising 224 children with acute hemorrhagic purpura, admitted to children's hospitals and the Epidemic Disease Hospital in Stockholm during the period 1946-1958. Forty-nine (22 %) of these patients presented renal symptoms in the initial phase. The risk for contracting renal complications was found to be statistically significant (5 % level) greater for boys than for girls. A total of 86 % of patients presenting renal symptoms initially became well within 1 year, and half already after 3 months. Only 5 of these patients showed signs of renal injury during the follow-up study, 2 with an observation period exceeding 5 years and 3 with an observation period of 1-3 years. Among the patients who initially failed to present any renal symptoms, 4 showed definite signs of

renal injury during the follow-up study while 4 others revealed suspicious signs of similar damage. Thus the late prognosis is just as good as in acute glomerulonephritis in children. Concerning the early prognosis it became apparent that the patients with abdominal symptoms and/or melena ran a considerably higher risk of getting renal complications than the patients presenting other symptoms. Patients with renal complications disclosed as a rule the regular symptoms looked for in the disease. The AST titers showed a trend toward normal or only slightly increased values even in patients with renal symptoms or in whom hemolytic streptococci had been demonstrated. These findings are quite the reverse of the usual high titers found in acute glomerulonephritis. An enhanced rate of infection susceptibility could not be detected. On the other hand, electrophoretic studies disclosed a hypogammaglobulinemia in a few cases.

DISCUSSION.—*C. G. Bergstrand:* The pathological changes are briefly discussed. Slight glomerular injuries were demonstrated in renal biopsy material. This work will be published in *Acta pædiat.*

B. Karlsson: Television epilepsy

It has been known for some time that optoelectric irritations may bring about epileptic attacks. This photogenic type of epilepsy is a favored study object in electroencephalography. Some cases have been reported in recent years of epileptic attacks being released by watching TV. The problems presented by TV epilepsy are illustrated by 5 investigated cases. In 4 of these patients the attacks were brought about while watching TV. One patient had a previously known epilepsy which had been completely controlled for 2 years with antiepileptic remedies; a new attack was released while watching TV. The attacks are usually induced by special circumstances connected with the TV performance, such as a quivering and jumpy picture or that the patient has been

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sitting too close to the TV screen in a completely darkened room. In 4 patients the EEG records have shown a photoconvulsive response to optic activation, with a general break-through of irregular spike and wave activity. Notable are the EEG findings during the resting curves of a case when a suggestive frontotemporal spike focus appeared which became accentuated during photostimulation. From a prophylactic point of view it is important to obtain pictures of good quality in TV. One might also attempt to prevent attacks by supplying the patient with special glasses reducing the light intensity and filtering out those portions of the spectrum which affect the patient most irritatingly.

A. Lundberg: Diagnostic value of different EKG leads in children

In routine examinations in pediatric cardiology of accidentally detected murmurs at the Children's Health Center or in school clinics, it is usually quite satisfactory to employ bipolar extremity leads. In dealing with evident organic heart defects or when something abnormal is disclosed by means of the standard leads, one needs registrations which supply more detailed information about the supposedly diseased organ. Precordial leads are usually employed ad modum Wilson. These will yield information about hypertrophy of the underlying cardiac muscle as f.ex. in pulmonary stenosis or pronounced pulmonary hypertension with increased load on the right ventricle in succession. The right-sided bundle block in the affected auricular septum is reflected by these leads, a finding which is not disclosed by means of the extremity leads, as in the above mentioned example. Changes in carditis and electrolyte disturbances likewise appear much more distinctly by means of these leads. The auricular activity is best studied via leads from the esophagus which passes along the rear of the heart at a distance of less than 1 cm. This method has long been employed in adult cardiology, but it would appear from available literature

that it has not as yet found its application in infants, in whom it should find its greatest usefulness in the study of the excessively frequent tachycardias observed especially during the neonatal period. The otherwise slight P waves attain a powerful amplitude in the esophageal registrations which afford a detailed study. From these one may ascertain the localization of the auricular ectopic center—facilitating a differential diagnosis between tachycardias induced in the auricle or the ventricle, which is valuable in the treatment of the patient. A detailed account is given of intracardial registrations from the auricle. However, these fail to supply more essential information about auricular arrhythmias than that yielded by the esophageal leads.

DISCUSSION.—*L. Lindgren:* It would be of considerable value before and during delivery to be able to differentiate between asphyxia produced by placental dysfunction or umbilical cord complications on the one hand and congenital heart failure of the fetus on the other hand. This is not possible by means of the usual auscultation of fetal sounds or by fetal phonocardiography. Neither is this possible with fetal EKG by means of abdominal leads, which only register the QRS complex. Ingelman-Sundberg & Lindgren succeeded in 1954 to elicit the complete PQRST complex by applying one electrode to the abdominal wall and one intrauterinely in contact with the leg of the fetus. Southern did likewise in 1957 by coupling in an extra amplifier to the abdominal lead and thus he was able to diagnose fetal anoxemia *in utero* by means of an inverted ST and a broadened T. The difficulty in eliciting the whole PQRST complex might be resolved by finding a suitable lead technic and by eliminating sundry noises which become further accentuated when the extra amplifier is attached.

G. Sterky and C. Thorén: Histamine analyses in a case of cold allergy

(Will be published in *Acta paediat.*)

M. d'Avignon, Stockholm

BOOK REVIEWS

Traitement du Diabète Infantile en Régime libre. Pierre Royer et Henri Lestrade.

Collection de Pédiatrie des Éditions Médicales Flammarion. Paris 1958, 194 pp. Price 3500 fcs.

This book introduces a new series of pediatric monographs under Professor Julien Marie's direction. Royer and Lestrade present here with commendable clearness and conciseness their experiences with more than 800 diabetic children admitted during a ten year period for treatment to l'Hôpital des Enfants-Malades in Paris.

In an introductory section dealing with the basis of diabetes therapy the authors discuss critically the older non-utilization respectively over-production theories and oppose these with ideas based on more recently acquired knowledge, which considers diabetic hyperglycemia as an expression of an "extracellular glucose-hypertension" caused by insulin insufficiency. Against the background of practical consequences entailed by this notion, the book makes a valuable contribution to the still continuing debate, regarding the choice of dietary treatment in juvenile diabetes. Nowadays this discussion is less preoccupied with the question of free diet or dietary restriction and more concerning to what extent the normal diet, which the diabetic child is allowed to eat, should be weighed and carefully controlled or not. Although the authors employ the term "régime libre" in the book's title, they make use in practice of a dietary treatment which, with certain modifications, they have chosen to call "régime normal non pesé". As a matter of fact the change is rather fluid from such a middle course to an unregulated free diet, on the one hand, and a strictly supervised normal diet, on the other hand.

Meanwhile the authors point out em-

phatically how important it is in this debate to check oneself from—which also is often done—confusing the question of dietary control with disease control. A watchful control of the diabetic disease is absolutely necessary and feasible, irrespective of the chosen type of diet. The criteria advanced by the authors for a good control are mainly those agreed upon nowadays by most diabetes therapeutic "schools", namely (1) normal diuresis, (2) absence of hypoglycemic reaction, (3) glycosuria which doesn't exceed 1 g/kg body weight or maximally 25 g per 24 hours, (4) blood-sugar variations between 80 and 250 mg%.

To the classical therapeutic triad of diet-insulin-exercise the authors add the extraordinarily important therapeutic aid which information and instruction of patients and their relatives entail, a field in which much remains to be accomplished.

Further an account is rendered in detail and with considerable acumen of different types of insulin therapy, treatment of acidosis and diabetic coma, complications of nutritive (Mauriac's syndrome) and vascular nature, social problems etc. Especially worthy of commendation is the very elegant and erudite presentation of the physio-pathological and therapeutic aspects of acidoketosis.

This book should be read by all physicians who are treating patients with juvenile diabetes.

Yngve A. A. Larsson, Stockholm

Diabetes Mellitus, with Emphasis on Children and Young Adults. T. S. Danowski, M.D.

William & Wilkins, Baltimore 1957, 510 pp. Price \$13.50.

While Royer & Lestrade's monograph mainly offers a personally colored, concise

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and intensive discussion of an important therapeutical problem, this book by Danowski constitutes a broadly conceived, objective and authoritative presentation of the diabetic disease from a theoretic as well as a clinical point of view. With its abundance of references this book therefore represents an invaluable handbook for the specialists and general practitioners desirous of acquainting themselves more profoundly with the different problems of the diabetes disease.

This work is divided into 3 principal parts: I. Biochemical and hormonal aspects, II. Manifestations, diagnosis, and therapy, and III. Developmental aspects and complications.

The first part presents fundamental facts bearing on the intermediary metabolism and its relation to hormonal factors in the adrenals, thyroid, pancreas, gonades, etc., and also about the present status in experimental diabetic research. The second part deals with certain fundamental clinical relationships, the symptomatology of the disease, hereditary factors, frequency rates, etc.; furthermore it treats of the characteristic electrolytic changes in connection with the administration of glucose and insulin, changes in the acid-base equilibrium in untreated diabetes, and essential therapeutic features.

On the question of dietary treatment the author favors the intermediate school of compromise between the restricted and the liberal dietary regimens. Thus he recognizes, on the one hand, the desirability to correct hyperglycemia and glycosuria to the greatest possible extent, while, on the other hand, he admits that this usually entails considerable difficulties in practice, and that one must try to avoid a high frequency of hypoglycemia, which beyond the acute risk may probably also exert a deleterious effect in the long run.

The author is most anxious to stress that the so-called normal diet of the non-diabetic population as a rule is too rich in calories and in animal fat, which probably contributes to the steady rise in cardiac and circulatory diseases. Control of the intake of calories and fat is therefore especially important in the treatment of diabetes mellitus. In short, this implies that the author prescribes diets which are first weighed and ultimately estimated, with a caloric intake enough to give satiety.

The last part of the book treats principally of the diabetic complications of acidosis, ketosis and coma, as well as of vascular, ocular and renal changes. Concerning the latter's etiology the author is dubious about the argument which contends that the degree of disease control and dietary restriction affects the rate of vascular lesions. He stresses that this is extremely high even in clinics pursuing a very rigid dietary regimen. We are inclined to agree with him that the linking together of disease control and rate of complications has greatly distracted clinicians and investigators from studies of alternative views. Other etiological possibilities might and ought to be considered.

In this connection the suggestion by Ditzel & Rooth, which is cited by the author, is interesting, namely that the micro-angiopathy in diabetes mellitus might represent a vasomotor reaction to variations in oxygen and carbon dioxide tension akin to that seen in retrolental fibroplasia. Whatever the case may be, the morphological similarities between retinal changes in retrolental fibroplasia and diabetic retinopathy are obvious.

Newer suggestions of this type may perhaps prove more fruitful than a continued discussion about the effect of different types of dietary management.

Yngve A. A. Larsson, Stockholm

ANNOUNCEMENTS

Two new periodicals in the field of Pediatrics

Two new journals of pediatric interest have appeared with their first issues and are heartily welcomed and recommended to pediatricians all over the world.

Cerebral Palsy Bulletin

is published by the National Spastic Society of London. The annual subscription price is 12/- (twelve shillings). The address is: The

General Secretary, National Spastics Society, 28 Fitzroy Square, London, W.L. England.

Biologia Neonatorum

is published by S. Karger, Basel/New York with Dr. A. Minkowski in Paris as chief-editor. Biologia Neonatorum is the continuation of "Etudes Néo-Natales", which was published since 1951 by the International

Children's Centre in Paris. The annual subscription price is Sw. fr. 25:—. One volume will consist of 4 numbers, issued quarterly. For subscription: S. Karger, Ltd., 25 Arnold Böcklin Strasse, Basel, Switzerland.

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From the Taylor Paediatric Research Laboratory, The Children's Hospital,
Sheffield, England

Brain and Adrenal Weight Relationship in the Later Stages of Intrauterine Life

by MORAG S. MACDONALD and JOHN L. EMERY

Morgagni, in the 17th century, was apparently the first to notice that the adrenal glands of anencephalic monsters were extremely small. His observation was later repeatedly confirmed (Ballantyne, 1902). Honan (1929) was the first to record careful weights in such infants, and in a series of seven children with anencephaly, the combined weights of the adrenals ranged from 0.9 to 3.5 g. This was contrasted with a series of eight children dying with hydrocephalus whose adrenal glands weighed from 5 to 8.5 g. He did, however, find two children with anencephaly having adrenal weights which he thought to be within the normal range. This association between anencephaly and small adrenals has interested many people, and the literature has been well summarised by Lanman and Baar. Much confusion has been introduced by a statement that the pituitaries are absent in anencephalic monsters (Moehlig), but Covell from a study of 32 cases of anencephaly showed that the pituitaries were within the normal weight range in infancy although they were often defective in the pars nervosa. We are thus left with an unexplained brain-adrenal relationship in

a gross type of growth deformity, i.e. agenesis of the brain. No corresponding relationship has been recorded between the adrenals and other anomalies (Tähkä).

The existence of a normal growth relationship between the development of the brain and the foetal adrenal cortex seemed possible, but in the assessment of such a relationship there are three main difficulties. First the post natal involution of the foetal adrenal cortex is sometimes extremely rapid and the weight of adrenals in children dying even a short time after birth can be an incorrect assessment of the foetal weight of the organ. We have found that the weight curves of the adrenals show a definite fall by the second day after birth. In some instances there appear to be involutionary changes even in stillborn children, and for this reason it is necessary to use only completely fresh stillborns and children who have died within 24 hours of birth.

The assessment of brain weights is subject to an error possibly in the opposite direction, in that oedema of the brain is common in infants dying within two to three days of birth. Thus the inclusion of children dying over the age of 24 hours is

likely to give rise to the double confusion of both oedematous brains and involuting adrenal glands. The great variation in the body size and organ weights of children of similar maturity means that any group will include large children with large brains and large adrenals, and the converse, making nonsense of any attempt at a direct relationship. We have attempted to overcome this difficulty by using a method of multiple analysis, using the crown-rump length of the child as a stabilising factor. The crown-rump length was used as it seems to be the single most accurately measurable aspect of an infant, not being susceptible to variation in water content and probably the best single measurement related directly to maturity.

Material and Results

The data used in this survey came from the records of necropsies carried out during the past few years at the Children's Hospital and City General Hospital, Sheffield. No selection was carried out, other than that all the required data were available, and that the infants were either fresh stillborns or died with no gross lesions of the brain or adrenal glands within 24 hours of birth. The "normality" of the organ was checked histologically. Eighty-four infants were used in the final analysis in this survey. The causes of death in these infants varied considerably. Many were due to placenta praevia and premature separation of the placenta, but although we have experience of examining something over 2000 such infant deaths, it is doubtful if we could honestly state the certain cause of death in half of these infants. We had intended to assess a much larger group of children in this study, but infants dying in this age group with no gross intracerebral lesions are not common. We were surprised when the pilot survey of 84 cases produced a statistically valid answer.

The statistical method adopted was to

plot the adrenal weights against the crown-rump length and the brain weight against crown-rump length of each case on two separate scatter diagrams. Regression lines were constructed on each diagram by the three group method of Gibson & Jowett (1957*a, b*), and the vertical distance of each point from the regression line was measured as a positive or negative value. The deviations of the brain and adrenal weights were plotted against each other on a third scatter diagram to obtain a comparison of brain weight with adrenal weight while holding the crown-rump length constant (Fig. 1). A regression line was constructed on this diagram, and this line is shown in the diagram. The regression coefficient b_{yz} was calculated from the details presented in Table 1 where \bar{x} and \bar{y} are the means of adrenal and brain weight deviations respectively. This gives $b_{yz} = +0.167$.

In order to assess the significance of this regression coefficient, the standard deviation was calculated from the vertical distance of the points from the regression line without regard to sign. The total deviation was 550.0 and the standard deviation 8.28.

The standard error of b_{yz} was obtained from the formula:

$$\begin{aligned} \text{Variance of } (b_{yz}) &= \frac{1}{nu} + \frac{1}{nl} \frac{(\text{standard deviation})^2}{(\bar{x}u - \bar{x}l)^2} \\ &= \frac{1}{21} + \frac{1}{22} \frac{8.28^2}{(35.25 + 28.4)^2} \\ &= 0.001576, \end{aligned}$$

giving standard error = 0.040.

t is found by dividing the regression coefficient by the standard error, i.e. $0.167/0.04 = 4.175$.

This result is highly significant indicating that the chances of the correlation being coincidental are less than 1/1000.

Discussion

It seems justifiable to conclude from the above results that, in infants surviving

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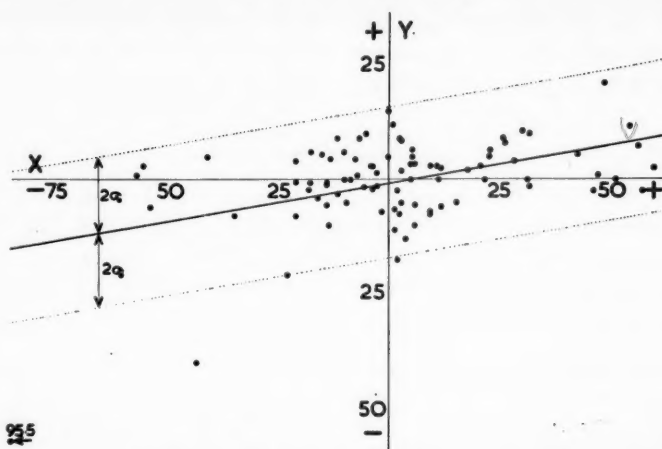


Fig. 1. Scatter diagram of the deviation of the brain and adrenal weights from their individual regression lines related to crown-rump length. The letters on the chart are referred to in the text.

TABLE I

Group	n	Means \bar{x}	\bar{y}	Slope of re- gression line $b_{yx} = \frac{(\bar{y}u - \bar{y}l)}{(\bar{x}u - \bar{x}l)}$
u: Cases with ad- renal weights more than 10g below the ex- pected level	22	-28.43	-6.43	$b_{yx} = \frac{10.62}{63.68}$
l: Cases with ad- renal weights more than 15g above the ex- pected value	21	+35.25	+4.19	$= +0.167$
Totals	84	+1.85	-0.55	

and that the clinical observation of minute adrenals in infants with anencephalus represents the one extreme of this relationship.

We have used the whole brain in this study, but it is likely that our findings reflect a more obvious correlation with some particular part of the brain, possibly the hypothalamus, but we do not, however, feel competent to isolate that area with sufficient accuracy for weighing. This would be particularly indicated from Covell's study of pituitaries from children with anencephaly; the small adrenals in his cases do not appear to be related to the anterior lobes of the pituitary, the only parts of the pituitary defective being the intermediate and posterior lobes.

In anencephalics the adrenals apparently develop normally for 5 months in utero, it being only in the later stages of growth that they lag in development (Nichols). This would suggest that the growth of the brain and adrenals are not determined by

less than 24 hours and in fresh stillborns, those having a high brain weight relative to their crown-rump length have similarly high adrenal weights, and the converse also holds, that infants with a relatively small brain have relatively small adrenals. This would support the concept that there is some common factor determining the growth of the brain and the adrenal gland,

each other, but are reflected by some outside factor, such as the placenta (Jones) or as others have suggested (Benirschke, Block & Hertig) determined by the placenta in early foetal life followed by the pituitary or hypothalamus later.

Summary

By means of a type of three-group regression analysis and using the crown-rump length as a stabilising factor, the weights of the brains and the adrenals have been studied from a group of eighty-four fresh stillbirths and children dying within 24 hours of birth. There appears to be a direct relationship between the brain and adrenal weight independent of the size of the infant.

Relation entre le poids du cerveau et celui des capsules surrénales dans les derniers stades de la vie intra-utérine.

Par une analyse régressive à trois variables utilisant la longueur du sommet de la tête au bas du dos comme facteur de pondération, les auteurs ont étudié les poids du cerveau et des capsules surrénales pour un groupe de quarante-deux enfants morts-nés ou décédés dans les vingt-quatre heures qui suivirent leur naissance. Il apparaît qu'il existe une relation directe entre le poids du cerveau et celui des capsules surrénales et que ce rapport est indépendant de la taille de l'enfant.

Das Gewichtsverhältnis zwischen Hirn und Nebennieren in den Spätstadien des intrauterinen Lebens.

Mit Hilfe einer Art von Dreigruppen-Regressionsanalyse und unter Anwendung der Scheitel-Steiß-Länge als Stabilisierungsfaktor wurde das Gewicht des Gehirns und der Nebennieren bei einer Gruppe von 84 totgeborenen bzw. innerhalb von 24 Stunden nach der Geburt verstorbenen Kindern studiert. Es scheint, dass eine unmittelbare Beziehung zwischen dem Hirn und Nebennierengewicht besteht, die von der Grösse des Kindes unabhängig ist.

Las relaciones ponderales cerebro-suprarrenales en los últimos estadios de la vida intrauterina.

Por medio del análisis de una regresión del tipo "tres grupos", utilizando la medida tronco-cabeza como factor estabilizador, fué estudiado el peso de cerebros y suprarrenales en un grupo de 84 niños, formado por nacidos muertos y niños que murieron dentro de las primeras 24 horas de vida. Parece existir una relación directa entre el peso del cerebro y de las suprarrenales, independiente de la talla del lactante.

Acknowledgements

Dr. G. H. Jowett, Head of the Department of Statistics of the University of Sheffield supplied the statistical tool for this study, and we have much pleasure in being able to acknowledge the debt that we owe to him and to Mrs Wendy Wright for their

advice. Much of the material used in this survey came from necropsies carried out at the City General Hospital Sheffield, through the courtesy of Dr. A. J. N. Warrack. Morag S. Macdonald is working under a grant from the Medical Research Council.

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The Taylor Paediatric Research Laboratory
The Children's Hospital
Sheffield, 10
England

Determination of Renal Concentration Capacity in Infants and Children without Renal Disease

by JAN WINBERG

Estimation of the kidney concentrating power is one of the most elucidating tests of renal function. The normal capacity in adults and older children is well established. As regards this function during the first year of life, however, most investigations have either been limited to the study of newborns (2, 8, 10, 18, 19) or has been based upon methods of examination hardly usable in routine clinical work (17).

During an investigation of renal function in acute urinary tract infections in childhood (22) it was found that accurate evaluation of the concentrating power in these cases necessitated an examination of the concentration capacity in normal infants, studied by methods imposing as little discomfort as possible on the patients.

In the present paper the results of the investigation of the renal concentrating power in 58 infants and children without known renal disease will be reported.

Material

The patients, 37 boys and 21 girls between the ages of 3 weeks and 14 years, were observed for conditions assumed to have no

significant influence upon renal function or upon water and electrolyte balance. They were all in good general condition.

Procedure

The concentrating power of the kidney, as demonstrated in Fig. 5, was determined by means of a test where a period of water deprivation was combined with the intramuscular administration of pitressin tannate in oil (Parke, Davis & Co). Since the diet given to infants usually is fairly constant as regards both protein and salt intake no special measures were taken to have the patients on a standardized diet. With the exception of the youngest child, none were breast fed at the time of the investigation.

The use of pitressin tannate involves a serious possibility of inaccuracy of dosage, which must be born in mind by those giving the injection. On standing the pitressin tannate may settle as a faint, brown precipitate, which may be left behind when the oil is sucked up into the syringe. The ampoules used were warmed in the hand and well shaken for 2-3 minutes. To diminish the risks of inaccurate dosage, ampoules where the precipitate was not easily suspended were discarded. Repeated microscopic checks of the distribution of the crystals in the oil showed this to be very uniform. Even when such small amounts of oil as 0.1 ml were given it seems probable that the pitresin dose was the desired one. The injection was

performed by means of a tuberculin syringe with 1/100 ml gradations.

The test was carried out in the following manner. The patients were on an ordinary ward diet before the test. At 4 p.m. pitressin tannate in oil was administered intramuscularly in a dose of 0.1 ml (0.5 pressure units) per 6 kg body weight. The evening meal was finished about 6 p.m. It consisted of formula or milk with bread and butter. No fluids or fruits were given until about 10 a.m. the following morning, when the same kind of food as the preceding evening was usually given. The patients were thus deprived of fluids for about 16 hours; (three patients below the age of 2 months for 10-12 hours only). No ill effects as a consequence of the experimental conditions were observed in any of the patients.

All urine specimens voided between 6 and 10 a.m. the day following the pitressin injection were collected separately, put into test tubes and stoppered as soon as possible. If only one or two urine specimens were saved before 10 a.m., urine collection was extended for some hours after the morning meal. In no cases were more than three specimens saved. The osmolality, and sometimes the specific gravity, were determined in all urine samples collected. Samples obtained within 30 minutes after the *beginning* of the first meal have been designated as urine samples obtained during the period of dehydration.

Laboratory Methods

The osmolality of urine was calculated from the freezing point depression determined by a thermistor and a resistance

bridge. With the apparatus used the osmolality was determined with a high degree of accuracy (Table 1).

The specific gravity was estimated either by means of an ordinary hydrometer, a correction of ± 0.001 being made for each 3°C variation above or below 15°C at which temperature the hydrometer was standardized, or, when only small amounts of urine were available, by weighing in pycnometers containing 3 or 10 ml. Before the weighing of the urine, the pycnometer was weighed filled with distilled water of the same temperature as the urine to be examined. Thus, no correction for variations in temperature was necessary.

There is no certain explanation for the fact that at like osmolalities urines where the specific gravity was estimated by a hydrometer were usually heavier than urines where the specific gravity was determined by weighing (Fig. 1). Since the former urines usually were 24-hour specimens and the latter in most instances samples obtained during the morning hours, the diurnal variation in composition may have played a role.

As can be seen in Fig. 1 the scatter of the specific gravity values corresponding to one and the same osmolal concentration may be very wide which is in accordance with the findings of Miles, Paton & de Wardener (16) and of Boyarsky & Smith (4). Corcoran (5) found a much better correlation between specific gravity and osmolality of urine. Since the concentration capacity of the kidneys is limited by the total number of dissolved particles, that is, the osmolal concentration, and not by the weight of the urinary solutes, the former is a more correct measurement of the concentrating power.

Results and Discussion

Before the result of the investigation of the concentration capacity in different age groups is presented, some aspects of the method used, pertinent to the evaluation of the data, will be discussed.

TABLE 1. Accuracy of double determinations of urine osmolality in 50 urine samples.

Difference between 1st and 2nd value (mOsm/kg H_2O)	0	3	6
Number of urines	31	13	6

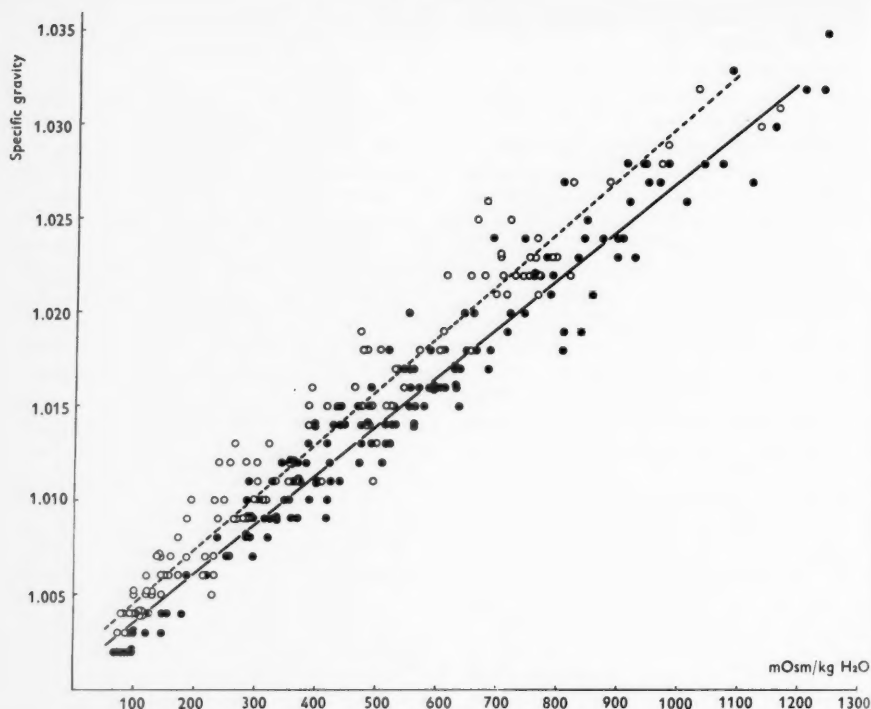


Fig. 1. Specific gravity as determined either by a hydrometer (----) or by weighing (—) plotted against osmolality.

$$---- y = 0.0000274 x + 1.00219$$

$$— y = 0.0000258 x + 1.00116$$

$$x = \text{mOsm/kg H}_2\text{O}. y = \text{specific gravity}.$$

Fig. 2. Influence of progressive dehydration and subsequent feeding on urine solute concentration in infants 2–11 months of age. The values are given in per cent of the highest osmolality observed *before* the end of the thirst period. The left part of the figure shows the urine solute concentration in 14 infants, who delivered at least two urine specimens between the 12th and 17th hour of water deprivation. The right part of the figure shows the urine solute concentration in 20 infants in whom at least one postprandial sample was obtained in addition to the preprandial one (ones). \times Concentration of the first urine specimen obtained. \circ The concentration of the urine specimen is higher than that of the preceding one. \bullet The concentration of the urine specimen is lower than that of the preceding one. \odot The concentration of the urine specimen is the same as that of the preceding one.

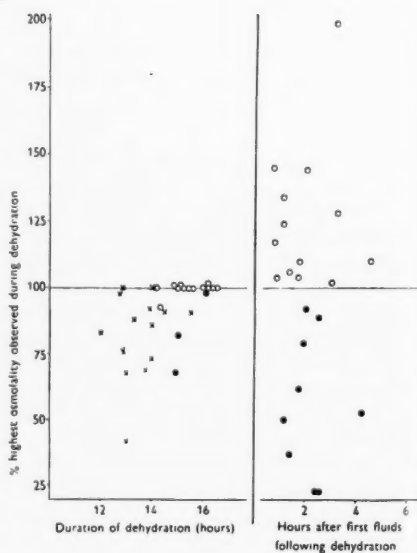


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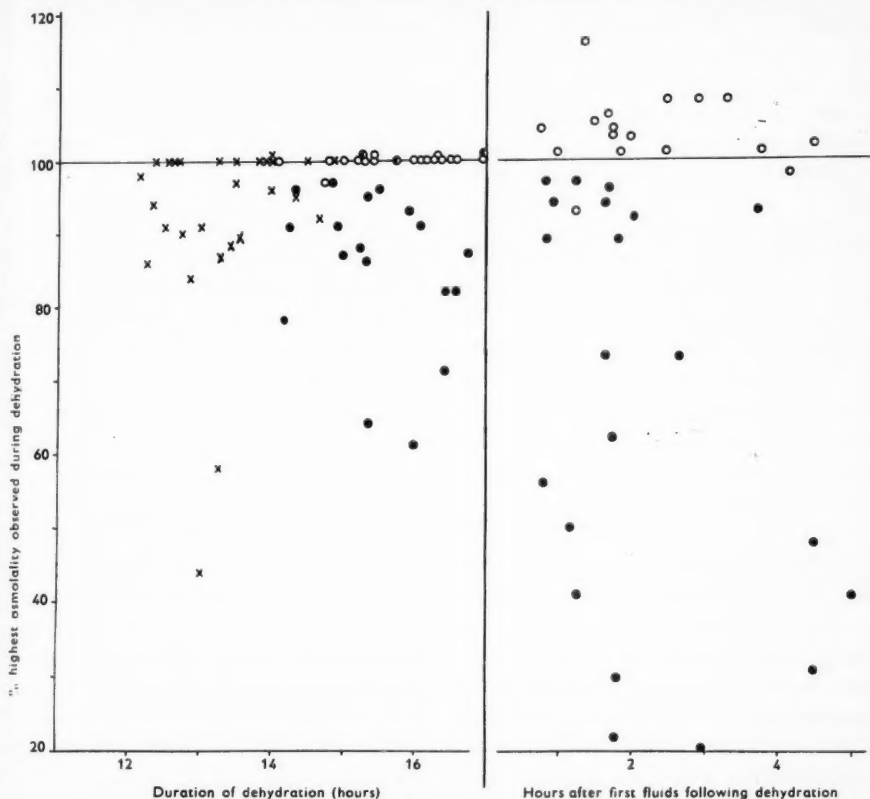


Fig. 3. Influence of progressive dehydration and subsequent feeding on urine solute concentration in 2-18 months old children given pitressin tannate in oil. Pitressin tannate was administered two hours before the thirst period began. The construction and legend are identical with Fig. 2. The left part of the figure shows the result of 28 experiments in 21 patients, the right part the result of 30 experiments performed in 26 patients.

Influence of the duration of dehydration on urine osmolality in patients not given pitressin tannate

Miles *et al.* (16) have suggested that in adults about 22 hours of water deprivation is necessary to obtain a relatively accurate idea of the kidney concentrating power. In infancy and early childhood such a long period of fluid withdrawal is impractical because of the great discomfort it will cause the patient. Fluid deprivation

for about 16 hours will, however, be relatively well tolerated if it includes the ordinary overnight thirst.

Fig. 2 shows the effect of progressive water restriction on urine solute concentration in infants 2-11 months of age. The values are given in per cent of the highest concentration observed during the period of dehydration. Since the first urine specimens obtained (x) were in most instances of lower concentration than the sec-

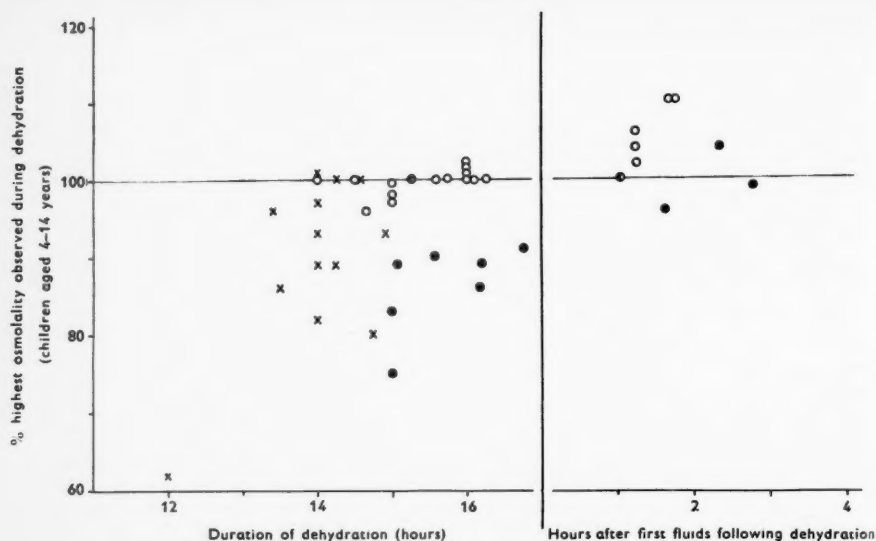


Fig. 4. Same experiment as in Fig. 3 performed in children 4-14 years of age. The construction and symbols of the figure are identical with those of Fig. 2. The left part of the figure shows the result of 13 experiments in 12 children, the right part the result of 8 experiments in 8 children.

ond or third ones (\circ ; \bullet) the figure suggests that there was a tendency for the concentration to increase between the 12th and 17th hour of dehydration, and in some instances even after the first post prandial fluids had been given. It is obvious that in several instances the actual concentration capacity was not even approached during the period of dehydration. Since patients of the age group investigated cannot deliver urine at fixed times the results of this kind of test may to a great extent become dependent upon when the patient voids his urine. This is a hazard that makes the test unreliable.

Influence of the duration of dehydration on urine osmolality in patients given pitressin tannate in oil

Fluids were withheld for about 16 hours as in the previous experiment, but in addi-

tion pitressin tannate in oil was administered 2 hours before the thirst period began. All patients were between 2 and 18 months of age. The result is shown in Fig. 3.

There was no general tendency for the urine solute concentrations to increase after the 12th hour of water deprivation. This suggests that there is a greater probability of obtaining a urine specimen with high solute concentration when a 12-17 hour period of water withdrawal is combined with the administration of pitressin tannate in oil than when it is not. This is an essential advantage when examining patients who deliver urine specimens at unpredictable times.

In children 4-14 years of age, also given pitressin, the findings were essentially the same as in the younger groups as regards the tendency to increase in osmolal con-

centration after the 12th hour of dehydration (Fig. 4).

The marked decrease in the osmolal concentration seen in some cases during the progressive dehydration will be discussed below.

Influence of fluids on urine osmolality in patients given pitressin tannate in oil

In adults under the influence of exogenous antidiuretic hormone, administration of large amounts of water does not cause any appreciable dilution of the urine (12, 20). This is in contrast to the reaction of some infants in the present investigation.

When formula was given to infants 18 hours after the administration of pitressin tannate, the feeding was often followed by a marked decrease in urine solute concentration (Fig. 3). A decrease to less than 60 per cent of the highest concentration, seen before the meal, was found in seven out of 10 patients below six months of age, only twice in 15 cases 6-22 months of age and in no case above 3 years of age. The findings might suggest that the decreased response of the kidney to exogenous antidiuretic hormone, shown to exist during the first weeks of life (1, 2, 10) may persist considerably longer. The findings preclude the use of pitressin tannate alone without simultaneous restriction of fluids in the determination of the concentration capacity in infants.

Irregular fluctuations of urine osmolality during progressive dehydration

It is shown in Figs. 3 and 4 that in some cases there may occur a considerable decrease of the urine osmolality during progressive dehydration. Very little is known

about the cause of such fluctuations. Hart & Verney (9) considered them often to be due to variations in posterior pituitary activity, but this does not seem to be a very probable explanation in patients under the influence of exogenous diuretic hormone (cf. 16).

It has been shown by Hinkle, Edwards & Wolf (11), Miles, de Wardener & Mc Swiney (14) and Miles & de Wardener (15), that emotional stimuli may cause a fall of the urinary solute concentration even greater than that observed in this investigation. Possibly the denial of food to a hungry infant may have acted as such a stimulus and been the direct cause of the decrease in urinary osmolality observed.

Uncontrollable influences on renal concentration capacity, such as those described, introduce a certain amount of hazard into the outcome of the test. This hazard can to some extent be eliminated by the saving of several urine samples, taking the one with the highest solute concentration as a measure of the actual concentrating power.

That the action of such undue factors in single instances may render the test totally unreliable is shown in Table 2. This 9 month old healthy infant passed, at the first examination, only urine of low concentration, but on repeated examination

TABLE 2. *Urine solute concentration after water deprivation plus pitressin (see text). Results of two examinations performed in the same child (age 9 months).*

Urine specimen number	I	II	III
Time of micturition (a.m.)	7.20	8.10	9.10
Osmolal conc. mOsm/l.	335	294	212
Time of micturition (a.m.)	6.30	8.05	8.50
Osmolal conc. mOsm/l.	1060	1172	1148

urine of very high concentration. Since it was obvious that in the first instance the concentrating mechanism did not work under optimal conditions, this result has been excluded from the material.

Reproducibility of the test performed as described under procedure

In 17 cases (16 below the age of 11 months) the concentration test was repeated after an interval of one to two weeks. The error in a maximum osmolal concentration value (standard deviation of one estimate) as determined by the method of double determinations (cf. 6) was 13.4 per cent (Table 3). The error

TABLE 3. Variation in double determinations of renal concentration capacity performed under standardized conditions (water deprivation plus pitressin, see text).¹

Mean diff. (D) (n)	s.d. _D	Error of method ² absolute per cent	Mean of de- terminations (range)
-26 ± 36 (17)	150	106 13.4	790 (560-1021)

arose from different influences on the concentration capacity, inherent in the method of investigation. This variation in double determinations performed under standardized conditions is relatively large, which is in accordance with the findings in adults deprived of water for 30 hours (16).

Changes in renal concentrating power with increasing age

The highest urinary solute concentration observed during the first pitressin

¹ Error of method determined according to method of double determinations. 2nd-1st value = D. s.d._D = standard deviation of differences. Error of method = s.d._D/√2.

² Standard deviation of one estimate.

test in each patient is plotted in Fig. 5. Since the values seemed, at inspection, to rise approximately logarithmically with increasing age, as is so often observed in functions of the growing child, the concentration values were plotted along a logarithmic time axis. As it has been shown by several authors (for relevant references cf. 21) that different aspects of renal function have reached their full maturation between two and three years of age, a regression line was calculated for the cases below three years of age, and a mean level for the cases above this age. As seen from Fig. 5, there is a large variation in the values around the regression line. However, it is obvious that there is an increasing concentration capacity, under the conditions given, up to an age of between one and one and a half years. The wide ranges found for the concentration capacity is a limiting factor in detecting minor degrees of concentration insufficiency in individual cases. The few determinations of the concentration capacity in infants below the age of two months make the range for the concentration capacity unreliable in this age group.

The regression lines should not be extrapolated to the neonatal period, since the observed data do not agree with the relatively high urinary solute concentrations occasionally seen during the first few days of life (2, 8, 10, 18, 19). In view of the recent demonstration made in dogs that a reduction in glomerular filtration is accompanied by an increase in the solute concentration of the secreted urine (3, 7), the hypothesis could be advanced that the relatively high urinary solute concentrations in newborns might possibly be due to the low glomerular filtration at this age

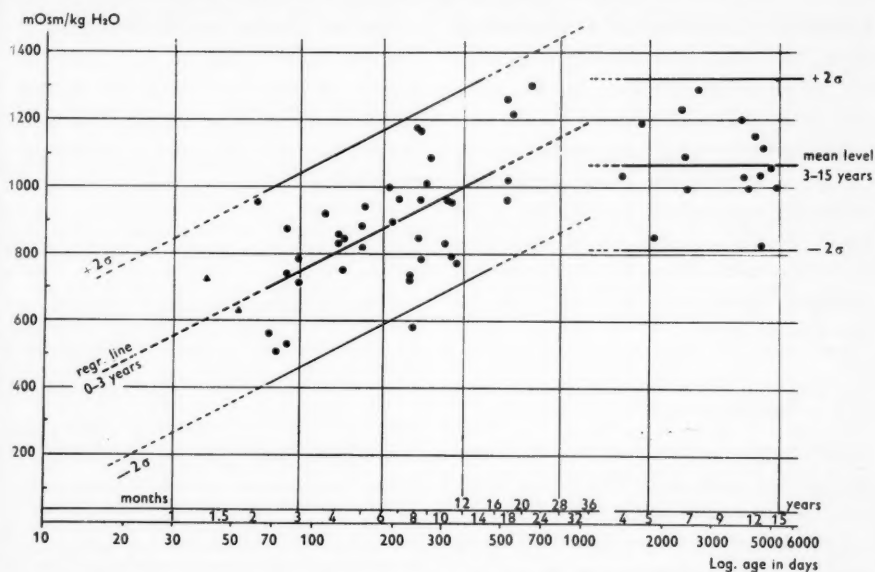


Fig. 5. Highest urine osmolality observed in the first pitressin test in each patient plotted against a logarithmic time axis. There seems to be an increase in the concentration capacity, under the conditions given, up to an age of between one and one and a half years. Because of the few determinations of the concentration capacity in infants below 2 months of age the ranges here are unreliable.

The regression line for children < 3 years: $y = 415.5x - 62.9$; $y = \text{mOsm/kg H}_2\text{O}$; $x = \log \text{ age in days}$; $r = 0.69 \pm 0.08$; s.d. around regression line = 145 mOsm/kg H₂O; $n = 42$.

The mean value for children > 3 years was 1069 ± 32 ; s.d. = 127.5 mOsm/kg H₂O; $n = 16$.

rather than to a well functioning concentrating mechanism.

Marquardsen & Jochims (13) have estimated the urinary specific gravity after fluid deprivation for 13-15 hours but without administration of pitressin. In 58 children 1-18 months old they also found the urinary specific gravity to increase with age. When their values were transformed into osmolal concentrations by means of the lower line in Fig. 1, many of them were found to lie considerably below those obtained in the present investigation. This suggests that deprivation of water for 13-15 hours often does not give true information concerning the actual

concentration capacity. This is in accordance with the findings related above (Fig. 2) suggesting a successive increase in urine concentration during the 12th to 17th hour of thirst without pitressin.

As regards the maximal renal concentration capacity during infancy Pratt, Bienvenue & Whyte (17) found values up to 1473 mOsm/kg H₂O in five infants one to two months of age. These authors fed their patients evaporated milk without additional water for one to five days. Their findings might support the opinion that the decreased renal concentrating power observed during infancy is not due to a renal inability to attain a high osmolal

U/P ratio but might be the consequence of other factors such as the composition of the ordinary infantile feed and the large volume of total body water.

The test devised in the present paper for the determination of the renal concentration capacity is carried out under relatively physiological conditions. Even if it does not define the concentration ceiling it seems to be serviceable in routine clinical work.

Summary and Conclusions

Difficulties met with in the determination of the urine concentration capacity in infants and small children are discussed.

It is shown that after a 12-16 hours long period of fluid deprivation the actual concentration capacity in many instances is not even approached.

It is further shown that administration of fluids to infants who are under the influence of exogenous antidiuretic hormone, may cause a considerable decrease in the urinary solute concentration. Thus the simple method of measuring the urine solute concentration after administration of exogenous antidiuretic hormone, which may be used in adults, is not applicable to infants.

A procedure for the determination of the kidney concentrating power of infants and children using a combination of dehydration and administration of pitressin tannate in oil is outlined.

Fifty-eight children without known renal disease were tested with this method. There seemed to be an increase in the concentration capacity up to an age of between one and one and a half years, when the adult range was reached.

The test may be used in estimating the function in renal disease, but subnormal values of the concentration capacity should be evaluated cautiously, since undue factors may influence the concentrating mechanism.

Mesure du pouvoir de concentration du rein chez des nourrissons et des enfants sans maladie rénale connue.

Cette étude expose les difficultés rencontrées lors de la détermination du pouvoir de concentration du rein, chez les nourrissons et les petits enfants.

Les résultats obtenus montrent qu'après une période longue (12 à 16 heures) de privation de liquides, le pouvoir maximum de concentration n'est pas atteint dans beaucoup de cas.

On peut également démontrer que l'administration de liquides à des enfants qui sont sous l'influence d'hormone antidiurétique exogène, peut provoquer une diminution considérable de la concentration urinaire. Par conséquent la méthode simple qui consiste à mesurer la concentration urinaire après administration d'hormone antidiurétique exogène et qui est utilisée chez les adultes, ne peut être employée chez l'enfant.

L'auteur décrit un procédé de détermination du pouvoir de concentration du rein; cette méthode utilise simultanément déshydratation et administration de tannate de pitressine en solution huileuse.

Cinquante huit enfants, sans maladie rénale connue, ont été étudiés à l'aide de cette méthode. Jusqu'à l'âge de 1-1½ an, on note une augmentation progressive du pouvoir de concentration; à cet âge il atteint les valeurs trouvées chez l'adulte.

Cette méthode peut être utilisée pour évaluer la valeur de la fonction rénale au cours d'états pathologiques; mais les valeurs anormales du pouvoir de concentration doivent être interprétées avec prudence: des facteurs exogènes peuvent influencer ce mécanisme.

Die Bestimmung der renalen Konzentrations-Kapazität von Säuglingen und Kindern ohne Nieren-erkrankung.

Die Schwierigkeiten bei der Bestimmung der Harn-Konzentrations-Kapazität von Kleinkindern werden besprochen.

Es wird gezeigt, dass nach 12-16-stündlicher Flüssigkeitseinschränkung die Konzentrations-Kapazität in vielen Fällen noch nicht erreicht ist. Es wird ferner gezeigt, dass die Gabe von Flüssigkeit bei Kindern, die unter dem Einfluss exogenen antidiuretischen Hormones stehen, zu einem beträchtlichen Abfall der Urin-Konzentra-

tion führen können. Deshalb ist die Gabe von exogenem antidiuretischen Hormon, die man bei Erwachsenen anwenden kann, bei Kindern nicht verwendbar.

Ein Verfahren, die Konzentrationsfähigkeit der Niere von Kindern unter Verwendung einer kombinierten Dehydration und Gabe von Pitresin-Tannat in Öl zu prüfen, wird skizziert.

58 Kinder ohne eine bekannte Nierenerkrankung wurden mit dieser Methode getestet. Dabei scheint ein Anstieg der Konzentrations-Kapazität bis zu einem Alter von 1-1½ Jahren, wo der Erwachsenenbereich erreicht wird, vorzuliegen.

Der Test kann zur Bestimmung der Funktion bei Nierenerkrankungen verwendet werden, jedoch müssen subnormale Werte der Konzentrations-Kapazität sorgfältig geprüft werden, da nicht renale Faktoren den Konzentrationsmechanismus beeinflusst haben können.

Determinación de la capacidad de concentración renal en lactantes y niños sin enfermedad renal.

Son discutidas las dificultades halladas en la determinación de la capacidad de concentración renal, en lactantes y niños pequeños.

Se demuestra como, aún luego de largos períodos, de 12 a 16 horas, de privación de fluidos, la verdadera capacidad de concentración no es determinable en muchos casos.

Se señala, además, como la administración de líquidos a lactantes que están bajo la influencia de la hormona antidiurética exógena, puede causar un descenso considerable en la concentración de solutos en la orina. Por lo tanto, un método tan simple, como sería la determinación de solutos en orina, aunque utilizable en adultos, no es aplicable en lactantes.

Se reseña un procedimiento de determinación del poder de concentración renal en lactantes y niños, usando un método combinado de restricción líquida y administración de Tanato de Pitresina oleoso.

Un grupo de 58 niños sin enfermedad renal conocida fueron sometidos a control por este método. Parece haber un ascenso de la capacidad de concentración hasta el año, año y medio, edades en que las cifras de los adultos son iguales.

Este test puede ser empleado en la estimación funcional durante el desarrollo de afecciones renales, pero los valores subnormales de la capacidad de concentración deberán ser valorados cuidadosamente, dado el gran número de factores capaces de influir sobre la regulación de la concentración urinaria.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

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Vascular Complications in Coarctation of the Aorta

by B. LANDTMAN and L. TUUTERI

Vascular complications are known to occur in patients with coarctation of the aorta. In materials collected before the advent of surgical treatment (1, 11) one third of the patients with this malformation had died of some vascular complication. Thus, 23 of 104 patients in Reifens-stein's series died of aortic rupture and 13 of intracranial vascular complications. More recently similar cases have been observed by several investigators (2, 3, 4, 5, 6, 8, 10, 12, 14) and the frequency of crippling complications and fatalities have been stressed by them.

In the Children's Hospital in Helsinki, 78 cases of coarctation of the aorta were seen during the time from 1953 to 1958. Ten of the patients were infants, 33 were 1-8 years and 35 9-15 years old. Vascular complications occurred in four cases. These cases will be presented and discussed.

Case Reports

CASE 1.—The patient was a boy of 11 years, the youngest of 3 children. There was nothing relevant in the family history. The mental and physical development of the boy had been normal. His exercise tolerance was normal and cyanosis had never been observed. Since the fall of 1954 the boy had often complained of headache. In the evening of March 8, 1955, he came home looking

tired and went to bed complaining of headache. Somewhat later the parents found him unconscious, his mouth twisted. In the morning a local doctor diagnosed right-sided hemiplegia and loss of speech. The patient was admitted to a local hospital and was transferred on the following day to a psychiatric hospital in Helsinki. On March 15, 1955, he was transferred to the Children's Hospital in the same town.

On admission the boy was conscious but could not speak. He could not move his right extremities, there was a partial facial palsy on the right side and a gaze paresis to the right. The right pupil was dilated. The tendon reflexes were symmetric except the right achilles which was exaggerated. The abdominal reflexes were weak on the right side. Babinski was positive on the right side. The apical beat was felt in the mid-clavicular line in the fifth intercostal space. A Grade 3 systolic murmur was heard at the left sternal border and in the back, where pulsating vessels were felt. The blood pressure in the right arm was 170/110, in the left arm 160/105 and in the legs 0 mm Hg. The femoral pulsations were not felt. The rest of the physical examination was non-contributory. Examination of the ocular fundi showed slight papillar edema on the left side. X-ray of the chest revealed a slight bulging of the left ventricle but no cardiac enlargement. Notching of the ribs were seen on both sides. ECG showed signs of left ventricular strain. Laboratory studies: hemoglobin 12.3 g%, erythrocytes 3.73 million, leucocytes 10,400 with 72 per cent

neutrophiles. The sedimentation rate was 25 mm/h. The cerebrospinal fluid was clear and the pressure was 220 mm H₂O. Nonne -, Pandy -, leucocytes 6, no erythrocytes, sugar 111 mg%, proteins 14 mg%. EEG showed pathologic tracings with large slow waves particularly in the left occipital region.

The condition gradually improved and one month after the onset of the hemiplegia the patient was able to walk when supported. He made little use of his right hand which was clumsy. He fully understood what he was spoken to but did not speak more than a few words. Concomitantly with the clinical improvement a normalization of the EEG tracings was observed although slight changes persisted in the left occipital region.

The boy was sent home for five months and he was readmitted on October 6, 1955. His general condition was now good but the spastic hemiplegia and the aphasia were unchanged. Bilateral carotid angiography was performed but did not reveal anything abnormal.

The coarctation was surgically corrected at the Children's Hospital on November 29, 1955. The coarctation was short and it was situated distally to the obliterated ductus arteriosus. Severe abdominal pains and symptoms of ileus developed during the first postoperative days. At the same time the systolic blood pressure in the arms remained 10 mm higher than before the operation. On the fourth postoperative day the blood pressure became normal and the recovery was uneventful.

Physiotherapy and speech exercises have been continued after the operation. In winter 1958 the boy walked freely but he still scarcely used his right hand. His vocabulary was limited to a few dozens of words and of them he could spontaneously use only a few. At this time the blood pressure was 120/70 mm Hg in the arms and 135/100 mm Hg in the legs.

CASE 2.—A boy of 6 years who was first admitted to the Children's Hospital on November 20, 1956. He was the older of two

children, his parents and the newborn sister were healthy. His development had been normal. A cardiac murmur was already heard at the maternity ward. No cyanosis was noted then or later. At the age of one year he was admitted to a hospital because of diarrhea and was then transferred to the Children's Hospital for cardiac examination. A blood pressure of 170 mm Hg in the arms was recorded and the femoral pulsations were not felt. The boy returned regularly for follow-up examinations to the Hospital.

On October 10, 1956, he fell hitting his cheek and developed a large local hematoma. No fractures were found at the municipal children's hospital and the recovery was uneventful. On November 20, 1956 the child was admitted to the Children's Hospital.

Examination showed a slender but healthy looking boy. The weight was 19.8 kg and the height was 112.5 cm. A Grade 5 systolic murmur and a Grade 2 diastolic murmur were heard at the left sternal border. Large pulsating vessels were seen and felt in the back. The blood pressure was 215/115 mm Hg in the left arm, 235/115 mm Hg in the right arm and 105/90 mm Hg in both legs. The rest of the physical examination was normal. X-ray of the chest revealed slight cardiac enlargement and prominence of the left ventricle. The aortic arch was small and a narrow segment was seen in its descending part. Notching of the ribs was seen on both sides. ECG showed left ventricular hypertrophy. Laboratory studies: Hemoglobin 11.5 g%, erythrocytes 4.27 million, mean corpuscular hemoglobin 27, leucocytes 5900, thrombocytes 200,000, sedimentation rate 10 mm/h.

At the operation which was performed on January 9, 1957 no communication was found between the upper and lower segments of the aorta. The arch ended into a blind sack distally to the origin of the left subclavian artery. The lower segment continued as a direct extension of a widely open ductus. The ductus was ligated and a side-to-end anastomosis was made.

The child's immediate postoperative condition was good. The blood pressure in the

arms decreased to 150/95 mm Hg and the femoral pulsations were strong. On the third postoperative day, however, the boy became febrile and tired and began to complain of abdominal pains. He remained subfebrile and the blood pressure increased on the sixth day to 180/135 mm Hg in the arms and 185/140 mm Hg in the legs. The abdomen was tender, slight ileus developed and a diffuse resistance could be felt on the right side. With conservative treatment the condition gradually improved although there still were occasional abdominal pains. Two months after the operation the boy was discharged in fairly good condition. The blood pressure was 145/115 mm Hg in the arms and 150/115 mm Hg in the legs.

The condition failed to improve at home and the abdominal pains persisted. The patient was readmitted to the Hospital six weeks after the discharge. Laparotomy was performed on April 2, 1957, and extensive intra-abdominal adhesions causing stricture of the terminal ileum were found and removed. One week later the condition again deteriorated and blood appeared in the stools. At relaparotomy performed on April 11, new adhesions were found orally from the site of the previous stricture. A necrotic and dilated segment of the small intestine was resected and a wide side-to-side anastomosis was made. The patient died in hyperpyretic shock 12 hours after the operation.

Histological examination of the ileum showed necrotizing arteriolitis and thrombosed arteries in the serosa and peritonitis. The rest of the autopsy was noncontributory.

CASE 3.—A boy, 11 years of age, the second of five children. There was nothing relevant in the family history. The delivery was normal and the development uneventful. A cardiac murmur was heard in infancy. Cyanosis had never been observed and the exercise tolerance was normal. In winter 1956 the school medical officer again heard the murmur but since the boy was free of symptoms no measures were taken.

In September 1957 the boy became pale and tired. A rise in temperature was first

noticed in October. He was admitted to a local hospital where marked anemia and a sedimentation rate of 56 mm/h were detected. There was persistent fever at 39°C. He received during 6 days a total of 6 million units of penicillin. On October 12, he was transferred to the Children's Hospital with the suspicion of bacterial endocarditis.

On admission he was pale, tired and subfebrile. The weight was 28.5 kg and the height 138.5 cm. There were a few small petechiae on the trunk. A Grade 2 systolic murmur was heard on both sides of the sternum and in the back, where pulsating vessels were felt. The femoral pulsations were weak. The blood pressure in the arms was 180/100 mm Hg and in the legs 85/? mm Hg. The liver was felt 5 cm below the costal margin. There was no enlargement of the spleen. The rest of the physical examination was noncontributory. X-ray of the chest showed the heart to be normal in size and shape. A narrow segment was seen in the descending aorta. There was no notching of the ribs. ECG showed incomplete right bundle branch block. Laboratory studies: hemoglobin 8.9 g%, erythrocytes 4.03 million, leucocytes 6800, thrombocytes 300,000, prothrombin time normal, sedimentation rate 73 mm/h. The blood culture was negative. Urine analysis was normal.

Since bacterial endocarditis was suspected intensive penicillin treatment was initiated. The condition improved, the temperature became normal and the liver decreased in size without digitalis. During the first week the blood pressure slightly increased; the systolic reading in the arms remained at 200 mm Hg.

The patient vomited a small amount of blood for the first time on November 2, 1957. There were no other symptoms save for slight abdominal pain. One week later, without preceding symptoms, he suddenly vomited large amounts of blood and fell immediately into deep shock. He recovered with blood transfusions but subsequently developed slight ileus, transitory signs of renal irritation and slight papilledema. Similar bleedings occurred on November 25

and on December 4 and 8. The condition remained otherwise practically unchanged. Nothing abnormal was found in the bleeding or clotting mechanisms of the blood.

On December 9, X-ray examination of the ventricle revealed a large contrast defect suggesting a tumor. Explorative thoracotomy was performed on December 11. However, the ventricle was found to be normal. In all probability the contrast defect had been caused by a blood clot. The venous pressure in the portal system was normal. After the patient had recovered from the operation esophagoscopy was made but apart from slight injection of the lower part of the esophagus nothing abnormal was detected. Some hours after the examination the patient again vomited blood and fell into deep shock. Resuscitation failed and the child died.

At autopsy the hemorrhage was found to be caused by rupture of a large collateral artery into the esophagus. The vessel, which originated from the aorta just below the coarctation, had perforated the esophagus at the level of the bifurcation. The coarctation was of the usual adult type. The remainder of the autopsy findings were non-contributory.

CASE 4.—A boy of 7 years, the second of two children. The sister and the parents were healthy. The delivery was normal and the child was immediately alert. Cyanosis had never been observed. The development had been normal. Slight shortness of breath was noticed when the child started to walk. Of late the symptoms had gradually increased. Coarctation of the aorta was diagnosed at the age of five years. The blood pressure then was 140/90 mm Hg in the arms and the femoral pulsations were not felt.

On admission on February 20, 1958, the general condition was good. The weight was 23.8 kg, and the height 127 cm. The color of the skin was normal. A Grade 3 systolic murmur was heard along the right and left sternal border and in the back where pulsating vessels were felt. The blood pressure in

the arms was 140/80 and in the legs 70/30 mm Hg. The femoral pulsations could not be felt with certainty. The rest of the physical examination was noncontributory. X-ray of the chest showed slight cardiac enlargement to the left. A segment of the descending aorta appeared narrow. The electrocardiogram showed left ventricular hypertrophy. Laboratory studies: hemoglobin 11.7 g, erythrocytes 4.72 million, leucocytes 5600, thrombocytes 200,000, sedimentation rate 5 mm/h. Urine analysis was normal.

The patient was operated upon on March 7, 1958. A short coarctation was found distally to the obliterated ductus arteriosus. Resection and end-to-end anastomosis were made without difficulties. The immediate postoperative condition of the patient was good. The femoral pulsations were strong but during the days following operation the blood pressure in the arms was slightly higher than preoperatively (140–165/115–130 mm Hg). Four days after the operation the patient began to vomit and complained of abdominal pain. Blood appeared in the stools on the tenth postoperative day and paralytic ileus developed. There was a rise in temperature and leucocytosis. One week later the boy became unconscious over a few hours. The cerebrospinal fluid was hemorrhagic. The condition remained unchanged and the patient died four days later without regaining consciousness.

At autopsy an extensive hemorrhage into the cerebral tissue destroying the major part of the left hemisphere was found. The origin of the bleeding was not found. There were no gross changes in the gastrointestinal tract or in other organs.

Discussion

Serious vascular complications in coarctation of the aorta are said to be comparatively rare in childhood. In Riefenstein's series (11) the group in which the cause of death was intracranial hemorrhage or aortic rupture included only three patients younger than 20 years. The risk

is usually mentioned when the prognosis of coarctation of the aorta and the optimal age for surgical correction are discussed. More recently, solitary cases of intracranial hemorrhage in children with coarctation of the aorta have been reported by different investigators (4, 9, 10, 12).

Cases of aortic rupture in coarctation of the aorta can be divided into two groups depending on whether the lesion is located distally or proximally to the coarctation. The former variety seems to be less common. A case of vascular rupture into the esophagus closely resembling the case in the present study has been described by Whyte & Lu (14). Solitary cases of similar dramatic complications have been observed by different investigators (2, 5, 8). All these cases were fatal.

Pathological changes in the vessel wall and hypertension have been considered causes for vascular complications in coarctation of the aorta. In some instances aneurysms have been found in the cerebral and intercostal arteries at autopsy (1, 4, 11). Aneurysms formed at the site of the poststenotic dilatation of the descending aorta are also possible sites for perforations.

The vascular complications which oc-

curred in the present series after successful surgical repair of the coarctation are difficult to explain. An unusual high incidence of abdominal pain following this operation have been reported by different investigators and in fatal cases necrosis and arterial thrombi have been found at autopsy (4, 7, 9, 13). The symptoms suggested that the abdominal pain was due to arterial spasm and ischemia that could progress to necrosis of the bowel wall. Sealy and his associates (13) were able to correlate these findings with a paradoxical rise in blood pressure after the operation. A similar postoperative rise in blood pressure was observed in two cases in the present series despite of the fact that the coarctation had been successfully repaired.

It is generally agreed that in patients with coarctation of the aorta the vascular bed in the lower part of the body is small because it has not been subjected to normal pressure. It is possible that a period of time is required for these vessels to adapt themselves to the increased pressure. The sudden release of pressure below the coarctation following surgery represents trauma which may give rise to vascular damage and local necrosis.

Summary

Vascular complications were seen in 4 of 78 children with coarctation of the aorta. In 2 of the cases the complications occurred after surgical correction of the coarctation. The complications were: Intracranial hemorrhage 2 cases, rupture of intercostal artery into the esophagus 1 case and mesenteric thrombosis 1 case. Three of the children died.

Complications vasculaires en cas de coarctation de l'aorte

Des complications vasculaires ont été observées dans quatre cas sur un ensemble de 76 enfants atteints de coarctation de l'aorte. Dans trois de ces cas, les complications survinrent après la correction chirurgicale de la coarctation. Ces complications vasculaires consistèrent en hémorragies intracrâniennes dans deux cas, en une rupture de l'artère intercostale dans un cas et en une thrombose mésentérique dans un cas. Trois de ces enfants sont morts.

Vaskuläre Komplikationen bei Aortenkoarktation.

Komplikationen von Seiten der Gefäße wurden bei 4 unter 76 Kindern mit Koarktation der Aorta beobachtet. Bei drei Fällen traten die Komplikationen nach operativer Korrektur der Koarktation auf. Die Verwicklungen waren folgende: intrakranielle Blutung bei zwei Fällen, Durchbruch einer Zwischenrippenarterie in die Speiseröhre bei einem Fall und Thrombose des Mesenteriums bei einem Fall. Drei dieser Kinder starben.

Las complicaciones vasculares en la coartación de la aorta.

En un grupo de 76 niños con coartación de aorta se vieron 4 casos de complicaciones vasculares. En 3 de los casos las complicaciones se presentaron luego de la corrección quirúrgica de la coartación. Estas complicaciones fueron las siguientes: Hemorragia intracraneana: 2 casos, Ruptura de una arteria intercostal en el esófago: 1 caso, y trombosis mesentérica: 1 caso. Tres de los niños fallecieron.

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University Children's Hospital
Stenbäcksgatan 11
Helsingfors
Finland

Respiratory Studies in Children

VII. A Longitudinal Study of the Lung Volumes in Asthmatic Children during Symptom-free Periods¹

by SVEN KRÆPELIEN

The prognosis of bronchial asthma in children has been a repeated subject of study. Flensburg (8) followed up 298 asthmatic children who received solely symptomatic treatment during 5-18 years of observation, but the attempt was made to eliminate environmental allergens as far as possible. He found that the asthma disappeared after an average of 7.4 years of illness in only 40 per cent of the children. The same material was re-examined by Ryssing (12) 13 years later. He found that, of 120 patients who were free from attacks at the time of Flensburg's examination, 59 had experienced symptoms again and 43 of them still had symptoms. He concludes that childhood asthma shows but little tendency to spontaneous cure and that only about 30 per cent of the patients become symptom-free after the age of puberty without specific treatment. Unger *et al.* (13), in a study of 306 specifically hyposensitized asthmatic children, recorded a figure of 32 per cent freedom from symptoms and 60 per cent

improvement after a period under observation of 1-30 years. Engström and Kraepelien (5) give corresponding figures of 26 and 58 per cent in a material consisting of 110 children who had received specific hyposensitization (2-4 years under observation). Rackemann and Edwards (11) found in a follow-up examination after 20 years of 449 asthmatics, who had received varying anti-asthmatic treatment (specific hyposensitization, vaccination, focal sanitation, etc.), that 71 per cent had become cleared of asthma in their teens (31 per cent "cured", 19 per cent no symptoms, but still sensitive, 21 per cent new symptoms, usually hay fever), and 15 per cent showed only mild symptoms.

All the investigations reported above were based primarily on the patients' subjective notion of their state of health, and secondarily on a general clinical examination. The reported results are difficult to compare because of the different criteria adopted for "freedom from symp-

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toms" and "improvement" in the various studies, and likewise of the considerable lack of uniformity in the observation periods and principles of treatment.

An objective record of changes in the patient's condition over a lengthy period would add to the assurance of the prognosis, especially in the individual case. Earlier in this series of respiratory studies in children it has been shown that a large group of asthmatics, even during symptom-free periods, show signs of changed pulmonary function, i.e. hyperinflation and disturbed ventilation (6, 7, 9). To obtain a more solid ground for assessment of the prognosis, it was considered of interest to follow the development during a certain period, in this case about 4 years, of the conditions of lung volumes in a group of asthmatic children who initially had pathological lung volumes during symptom-free intervals, and at the same time to follow their general clinical development.

Definitions, Nomenclature and Methods

These are set forth in the first paper in this series of respiratory studies in children (4).

Material

The material for this study came from in-patient and out-patient departments for allergic children at the Pediatric Clinic of Karolinska Sjukhuset and from the Sachs' Children's Hospital, Stockholm. For the purpose of the study 20 asthmatic children were selected from a number who, some 18-24 months earlier, had manifested an elevation of the ratio of residual volume to total lung capacity (V_R/V_{TLC}) during symptom-free periods and whose clinical status was such that symptom-free periods occurred. All these children were included

in the material reported earlier by the author and coworkers, "Respiratory studies in children. II. Lung volumes in symptom-free asthmatic children, 6-14 years of age" (9) in which 50 out of 98 children had a V_R/V_{TLC} above the 95 per cent confidence interval for healthy children. As is seen from Table 1, at the first examination (Series A) all children had a V_R/V_{TLC} above the 95 per cent confidence interval for healthy children (0.158-0.276); in the majority, moreover, the ratio of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) was also above the 95 per cent confidence interval for healthy children (0.355-0.503). In selecting patients for this study only such children were accepted as might be expected to be available for continuous observation with the cooperation of the children themselves and of their parents during the next few years. As will be seen from Table 1, there was some variance in the degree of severity of asthma, judged by the frequency of attacks. Two children have been excluded from the primary material owing to technical accidents during the second examination (Series B). The remaining 18 children (9 boys and 9 girls) were all examined twice (Series A and B) and 16 children (8 boys and 8 girls) a third time (Series C). The Series A examination was conducted during the period July 1954 to July 1955, Series B November to December 1956, and Series C September to December 1958. The interval between the first and second examination was thus 17-28 months, and between the first and third 43-51 months (Table 1).

The age of the children at the time of the first examination varied between 6 and 12 years. The age distribution is shown in Table 1. The physical development of the children during the period covered by the investigation was assessed on the basis of age, height and weight. With the exception of one girl in Series C, all children at the various examinations were within the values for normal children given by Broman, Dahlberg & Lichtenstein (1). All children were well-known to the examiner. They came in for regular examinations throughout the

TABLE I.

Case no.	Sex	Age at onset of asthma, years	Time intervals in years		V_R/V_{TLC}			V_{FRC}/V_{TLC}			Treatment (S = specific hyposensitization)	Severity of asthma* at		
			A-B	A-C	A	B	C	A	B	C		A	B	C
1	F	3	10 $\frac{10}{12}$	—	0.37	0.34	—	0.60	0.53	—	Repeated Allergol cures 1949-51, S. 1951-57.	III	I	II
2	M	3	12 $\frac{10}{12}$	2 $\frac{2}{12}$	0.28	0.22	0.21	0.52	0.52	0.50	S. 1954-56.	I	I	I
4	F	7	11 $\frac{12}{12}$	2 $\frac{12}{12}$	0.34	0.32	0.30	0.56	0.57	0.48	S. 1953-56, Abrasio 1954.	I	I	I
5	M	2	8 $\frac{12}{12}$	2 $\frac{2}{12}$	0.28	0.23	0.20	0.53	0.51	0.46	S. 1954-57.	II	I	I
6	M	3	8 $\frac{12}{12}$	2 $\frac{12}{12}$	0.30	0.35	0.17	0.51	0.51	0.47	Abrasio 1952, S. 1955-.	III	II	II
7	F	2	8 $\frac{12}{12}$	1 $\frac{12}{12}$	0.31	0.24	0.22	0.51	0.55	0.56	Allergol cure 1955.	II	I	I
8	M	3	6 $\frac{12}{12}$	2 $\frac{12}{12}$	0.30	0.24	0.24	0.52	0.51	0.47	Allergol cure 1953, S. 1954-58.	I	I	I
10	F	1	8 $\frac{12}{12}$	1 $\frac{12}{12}$	0.29	0.19	0.19	0.50	0.39	0.40	Repeated Allergol cures 1949-54, Anticatharr vaccine 1951-52.	I	I	I
11	F	4	6 $\frac{12}{12}$	2 $\frac{12}{12}$	0.36	0.18	0.21	0.49	0.37	0.37	S. 1954-57.	I	I	I
12	M	5	7 $\frac{12}{12}$	2 $\frac{12}{12}$	0.32	0.28	0.27	0.46	0.47	0.50	S. 1954-57 and 1958-., Anticatharr vaccine 1951-52.	II	I	I
13	F	1	7 $\frac{12}{12}$	2 $\frac{12}{12}$	0.41	0.28	0.18	0.52	0.46	0.41	S. 1951-53 and 1954-55, Steroid treatment in summers 1955 and 1956.	III	I	I
14	M	2	11 $\frac{8}{12}$	1 $\frac{12}{12}$	0.31	0.27	0.25	0.51	0.51	0.49	Abrasio 1947, S. 1955-., Anticatharr vaccine 1956-.	III	II	I
15	F	4	9 $\frac{12}{12}$	3 $\frac{12}{12}$	0.35	0.32	0.28	0.53	0.53	0.46	S. 1951-54 and 1955-57.	III	II	II
16	F	2	6 $\frac{12}{12}$	2 $\frac{12}{12}$	0.36	0.19	0.14	0.54	0.44	0.41	S. 1951-54.	I	I	I
17	M	1	10 $\frac{10}{12}$	1 $\frac{12}{12}$	0.40	0.31	—	0.54	0.47	—	S. 1955-.	I	I	II
18	M	3	8 $\frac{12}{12}$	2 $\frac{12}{12}$	0.28	0.21	0.21	0.47	0.46	0.43	S. 1949-51 and 1952-56, Abrasio 1955.	I	I	I
19	F	5	11 $\frac{12}{12}$	4 $\frac{12}{12}$	0.39	0.26	0.27	0.54	0.46	0.46	S. 1953-.	III	I	II
20	M	4	11 $\frac{12}{12}$	2 $\frac{12}{12}$	0.30	0.25	0.23	0.46	0.51	0.45	2 Allergol cures 1952, S. 1953-56.	II	I	I

* Classification of asthma: Group I: Mild asthma with less than 5 short attacks a year; Group II: Moderately severe asthma with 5-10 attacks a year; Group III: Severe asthma with more than 10 attacks a year, or prolonged status asthmaticus.

investigation period. Uniform principles of treatment were employed. Cases revealing a manifest allergy in allergological examination (based on anamnesis, allergic test and provocation test) were given specific hypsensitization treatment with one or more allergens during the investigation period, or had received such treatment earlier. Certain cases, in which no causative agent could be traced, received non-specific treatment either with colloidal sulphur (Allergol) or anticatarrh vaccine. Focal sanitation was performed when indicated. As far as possible, environmental control of all cases was carried out on normal allergological principles, and symptomatic treatment was given during periods of asthmatic attacks (steroid therapy was administered only in Case 13 during two summer seasons). The treatment for the entire material is summarily presented in Table 1.

All children were entirely free from asthmatic symptoms on all occasions of examination and had received no symptomatic treatment for at least three days before each examination. Two children (Cases 1 and 17) had to be excluded from Series C since they could not be freed from symptom at the time of that examination without symptomatic treatment.

Random Error of the Method

Since the three series of examinations, A, B and C, were conducted at intervals of about two years, the error of the method has been calculated for each series separately. The reasons for this procedure were that the apparatus was slightly modified during the period, and that the examinations were not performed by the same personnel. The random error of the method for each lung volume was calculated from the differences between duplicate determinations by the method evolved by Dahlberg (3). The *t*-test between the methodic errors for the respective volumes in the various series showed no significant difference, for which reason Series A, B and C, may be considered comparable and have been lumped together in the statistical

analysis. The variation coefficients prove to be of the same order of magnitude as in earlier investigations (4, 9, 10).

Results

As in earlier publications in this series of respiratory studies in children, the lung volumes (V_R , V_{FRC} and V_{TLC}) have been related to body height, and the ratios to age. The ratios V_R/V_{TLC} and V_{FRC}/V_{TLC} for the different examinations are set forth in Table 1.

In the statistical analysis the respective volumes and ratios were initially considered on a group basis. A regression calculation was carried out and the resulting regression lines are shown graphi-

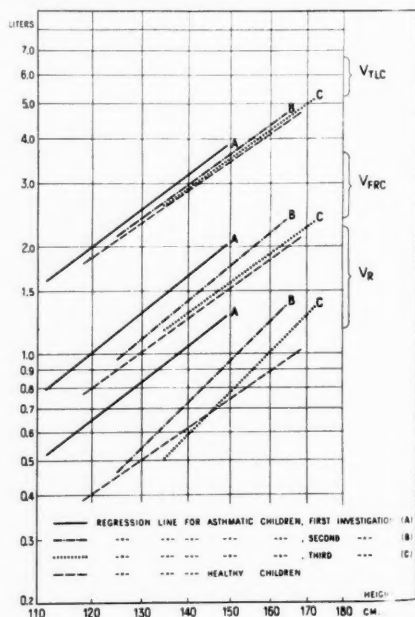


Fig. 1. Regression lines for total lung capacity (V_{TLC}), functional residual capacity (V_{FRC}) and residual volume (V_R) in relation to height at the various examinations (A, B and C). The regression lines for healthy children are also shown.

TABLE 2. *Results of covariance analysis.*

Difference between ...	Series A - Healthy children	Series B - Healthy children	Series C - Healthy children	Series A - Series B	Series A - Series C
V_R					
Slope	$P > 0.05$	$P < 0.01$	$P < 0.01$	$P > 0.05$	$P > 0.05$
Distance	$P < 0.001$	$P < 0.01$	$P > 0.05$	$P < 0.001$	$P < 0.001$
V_{FRC}					
Slope	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Distance	$P < 0.001$	$P < 0.01$	$P > 0.05$	$P < 0.01$	$P < 0.001$
V_{TLC}					
Slope	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Distance	$P < 0.01$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P < 0.01$
V_R/V_{TLC}					
Slope	$P > 0.05$	$P < 0.01$	$P < 0.01$	$P > 0.05$	$P > 0.05$
Distance	$P < 0.001$	$P < 0.001$	$P > 0.05$	$P < 0.001$	$P < 0.001$
V_{FRC}/V_{TLC}					
Slope	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Distance	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.01$	$P < 0.001$

cally in Figs. 1 and 2 with the corresponding lines previously found for healthy children. Judging from the distances between the lines, there has been a successive normalization between the first, second and third examination. The significances of the distances between the lines were statistically investigated by covariance analysis (Table 2). As the table shows, there are statistically significant differences in distances for all volumes and ratios in Series A and B compared with healthy children, with the exception of V_{TLC} in Series B. There are likewise statistically significant distances between the lines for Series A and B, except in the case of V_{TLC} . Between Series A and C there are significant differences for all volumes and ratios. As regards Series C, there are no significant differences to the regression lines for healthy children except in the ratio V_{FRC}/V_{TLC} .

The difference in slope between the various lines has also been assessed statisti-

cally (Table 2). Significant differences were found for the V_R lines only when comparing healthy children with Series B and C.

So far the material has been considered as a group. But a statistical analysis was also made of the variations in the individual at the successive examinations. As the lung volumes increase with body growth an account must be taken of the individual's physical development, and the analysis was done as follows. For each individual the values of the lung volumes (logarithmic) and the values of ratios at the first examination were compared with the corresponding values for healthy children of the same height and age respectively, obtained from the regression lines for healthy children. The differences (a) in each lung volume and ratio have been calculated. In the same way the differences were determined between the values for each individual at the second and the third examinations and

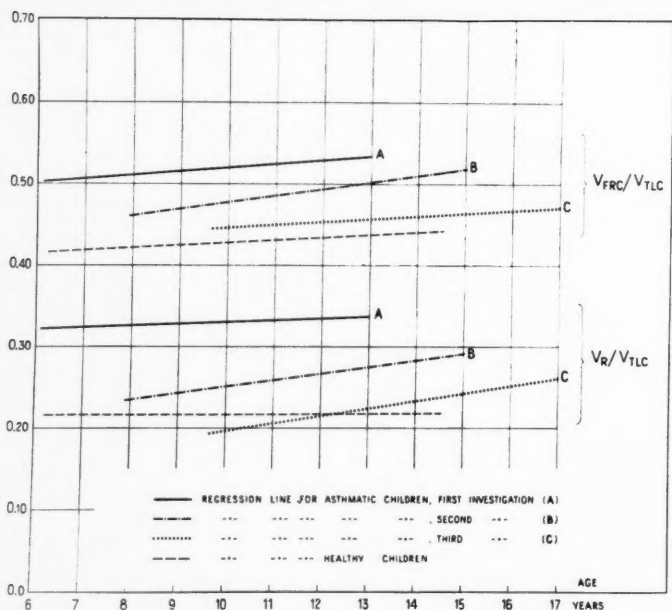


Fig. 2. Regression lines for the ratios of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) and residual volume to total lung capacity (V_R/V_{TLC}) in relation to age at the various examinations (A, B and C). The regression lines for healthy children are also shown.

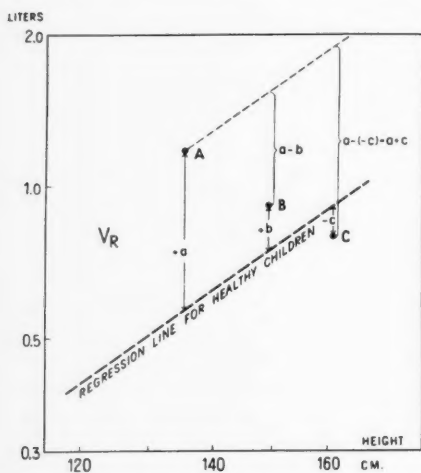


Fig. 3. Schematic representation of the method of statistical analysis, taking into account changes in one individual (Case 13).

the corresponding reference points for healthy children (b and c). The method of calculation is shown schematically for V_R in one case in Fig. 3. The means of a and b for the various lung volumes (V_R , V_{FRC} and V_{TLC}) and ratios (V_R/V_{TLC} and V_{FRC}/V_{TLC}) have been calculated and tested against zero and found significant for all volumes and ratios except for V_{TLC} in Series B (Table 3). The corresponding tests for c , on the other hand, show no significant difference for any volume or ratio. The differences between the volumes and ratios of symptom-free asthmatic children in relation to those of healthy children at the various examinations expressed in percentage are shown in Table 3. Furthermore the differences $a-b$ and

TABLE 3. The percentual mean differences between lung volumes and ratios of symptom-free asthmatic children compared with those of healthy children at the various examinations (A, B and C), taken into account individual progress.

Mean diff., % ...	Series A - Healthy children <i>a</i> (<i>t</i> -test)	Series B - Healthy children <i>b</i> (<i>t</i> -test)	Series C - Healthy children <i>c</i> (<i>t</i> -test)	Series A - Series B <i>a</i> - <i>b</i> (<i>t</i> -test)	Series A - Series C <i>a</i> - <i>c</i> (<i>t</i> -test)
V_R	67.0 $P < 0.001$	25.3 $P < 0.01$	4.6 $P > 0.1$	34.1 $P < 0.001$	55.2 $P < 0.001$
V_{FRC}	29.1 $P < 0.001$	20.9 $P < 0.001$	4.2 $P > 0.1$	6.9 $P < 0.01$	20.4 $P < 0.01$
V_{TLC}	10.0 $P < 0.01$	3.7 $P > 0.1$	0.9 $P > 0.1$	6.0 $0.05 > P > 0.02$	6.8 $P < 0.05$
V_R/V_{TLC}	51.5 $P < 0.001$	19.8 $P < 0.01$	3.7 $P > 0.1$	31.8 $P < 0.001$	45.2 $P < 0.001$
V_{FRC}/V_{TLC}	21.2 $P < 0.001$	12.6 $P < 0.001$	4.8 $0.1 > P > 0.05$	8.4 $P < 0.01$	14.4 $P < 0.001$

$a - c$ were calculated (see Fig. 3) for each individual case and the means of these differences were calculated and tested against zero (Table 3). Significant differences were found for all volumes and ratios except for V_{TLC} . The statistical analysis accordingly shows that a successive normalization of the conditions has occurred between the different examinations. Table 3 shows that V_R is the first of the lung volumes measured to be normalized.

Discussion

In a cross-sectional study of symptom-free asthmatic children, considered as a group, the authors and his coworkers found an elevated V_{FRC} and V_R , indicating hyperinflation of the lungs both during quiet breathing and after maximal expiration. This hyperinflation may conceivably be caused by a temporary bronchial obstruction of functional origin and, or alternatively, by a real emphysema, by which is meant "a pathological condition of the lung characterized by reduction or loss of elastic fibres, tearing of alveolar septa, and decrease in the pulmonary capil-

lary bed" (2). Earlier in this series it was found that the administration of various bronchodilator drugs reduces the degree of hyperinflation, suggesting that it is, at least to some extent, of a functional character (10).

The results of the investigation, in which the lung volumes of asthmatic children in symptom-free periods were followed for some years, show that the hyperinflation has successively diminished. This is equally true whether the material is considered as a group or whether attention is paid to individual changes. At the last examination—about four years after the first—the lung volumes of the asthmatic children differed only slightly from those in healthy children. The results for Series C would probably have been rather less favourable if the two children had been included who, at the time of the examination, had a period of more or less continuous attacks, and could not be freed from symptoms without symptomatic treatment. Nevertheless the successive reduction of hyperinflation to practically normal lung volumes suggests that the marked hyperinflation in this group of

symptom-free asthmatic children at the first examination was of functional origin and therefore reversible.

If we compare the lung volume results with the clinical assessment of the children's state of health and their progress during the investigation period, the two pictures are closely analogous. This is illustrated in Table 1 by the severity of the asthma, based on attack rate, during the year prior to each examination. As the table shows, the attack rate successively diminished in 8 out of the 18 cases. Seven other cases, classified as mild asthma (Group I) at all examinations, also showed clinical improvement. The reason for keeping these cases in Group I is that, despite their complete freedom from symptoms during one or more years, we still do not feel justified in classing them as fully healthy. Three cases (1, 17 and 19) underwent clinical exacerbation during the last year, and it is two of these cases (1 and 17)

which were excluded from Series C. Taking a broad view of the progress of the illness in each patient during the last five years from general clinical considerations, without strict attention to the classification by severity of asthma, all cases except one (Case 17) underwent successive improvement.

It is not possible to draw any general conclusions as to the prognosis of bronchial asthma in children from the present investigation. Even if there is good correlation between the clinical course and the normalization of the lung volumes a remaining disturbance of ventilation, cannot be excluded. Although this is possible in certain cases, the reduction or almost entire disappearance of the hyperinflation which previously existed, as was the case in this material, must be regarded as a favourable development, since permanent hyperinflation gradually opens the way to parenchymal injury as in emphysema.

Summary

1. The lung volumes of 18 asthmatic children (9 boys and 9 girls) with initially elevated ratio of residual volume to total capacity were re-examined during symptom-free periods after intervals of about two and four years.

2. In these later examinations the original hyperinflation had successively diminished, and at the last examination the lung volumes did not differ markedly from those of healthy children.

3. The general clinical improvement observed in the children between the first and last examination was closely analogous to the changes in lung volumes demonstrated during the same period.

4. The results suggest that the hyperinflation demonstrated earlier is of functional origin and thus reversible. The successive normalization of the lung volumes is a hopeful sign from the prognostic aspect.

Etude de la respiration chez l'enfant. VII. Etude prolongée des volumes pulmonaires chez les enfants asthmatiques durant les périodes libres de symptômes

1) Les volumes pulmonaires de 18 enfants asthmatiques (9 garçons et 9 filles) chez qui l'on avait initialement trouvé un rapport élevé du volume d'air résiduel par rapport à la capacité totale furent réexaminés au cours de périodes libres de toute manifestation clinique et après des intervalles approximatifs de 2 et 4 ans. 2) A l'occasion de ces examens ultérieurs, il fut constaté que le « soufflage » initial avait progressivement diminué, et lors du dernier contrôle les volumes pulmonaires ne différaient pas sensiblement de ceux observés chez les enfants bien portants. 3) L'amélioration générale de l'état clinique observée chez ces malades au cours du délai séparant le premier examen du dernier, fut assez strictement superposable aux modifications enregistrées dans les chiffres des volumes pulmonaires durant la même période. 4) Ces résultats donnent à penser que le « soufflage » initialement constaté a une origine fonctionnelle et qu'il est, de ce fait, réversible. La normalisation des chiffres des volumes pulmonaires est un signe encourageant sur le plan du pronostic.

Atmungsstudien bei Kindern. VII. Eine Längsschnittstudie der Lungenvolumina bei Asthma-Kindern während symptomfreier Perioden

1) Die Lungenvolumina von 18 Asthma-Kindern (9 Jungen und 9 Mädchen) mit initial erhöhtem Verhältnis vom Residualvolumen zu totaler Lungkapazität wurden während der symptomfreien Perioden nach zwei- und vierjährigem Intervall nachuntersucht. 2) Bei diesen letzten Untersuchungen hat sich die ursprüng-

liche Hyperinflation sukzessiv vermindert; bei der Untersuchung nach ungefähr vier Jahren unterschieden sich die Lungenvolumina nicht wesentlich von denen gesunder Kinder. 3) Die allgemeine klinische Besserung, die an den Kindern zwischen der ersten und der letzten Untersuchung beobachtet wurde, war in hohem Masse analog den Veränderungen der Lungenvolumina der gleichen Beobachtungsperiode. 4) Das Resultat lässt vermuten, dass die demonstrierte Hyperinflation funktionell bedingt und somit reversibel ist. Die sukzessive Normalisierung der Lungenvolumina ist — prognostisch gesehen — ein günstiges Zeichen.

Estudio de la respiración en la infancia. VII. Estudio longitudinal del volumen pulmonar en niños asmáticos durante los periodos asintomáticos

1) Durante periodos libres de síntomas, y con intervalos de 2 a 4 años aproximadamente, fueron reexaminados los volúmenes pulmonares en 18 niños asmáticos (9 niños y 9 niñas), que presentaban una relación de volumen residual a capacidad total inicialmente elevada. 2) En estos últimos exámenes la hiperinsuflación original había disminuido en forma sucesiva, y en el último examen, los volúmenes pulmonares no diferían notablemente de los hallados en niños normales. 3) La mejoría clínica general, observada entre el primero y el último examen, mostró una estrecha semejanza con los cambios en el volumen pulmonar demostrados en ese mismo periodo. 4) Los resultados sugieren que la hiperinsuflación primeramente demostrada es de origen funcional, y por lo tanto, reversible. La normalización sucesiva del volumen pulmonar, es un signo favorable del punto de vista pronóstico.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

From the Department of Metabolic Research (Head: H. Boström), Wenner-Gren Institute, University of Stockholm, and the Medical Department IV (Head: S. Kallner), Södersjukhuset, Stockholm

Cystinuria in Sweden

II. The Incidence of Homozygous Cystinuria in Swedish Schoolchildren

by HARRY BOSTRÖM and KERSTIN TOTTIE

Many discrepant reports on the incidence of cystinuria are to be found in the literature. To some extent, the differences in the results obtained by different workers (10, 14, 16), briefly summarized in Table 1, may be ascribed to differences in the distribution of this syndrome in the various populations investigated. The chief reason for the lack of conformity in the results reported in previous studies seems, however, to be the use of methods not specific enough for a proper diagnosis, and the classification of individuals with a raised excretion of cystine on the sole basis of analysis of urine samples.

Our knowledge of cystinuria has increased markedly in the past 10 years, through the extensive studies made by different groups of workers, employing microbiologic, chromatographic and polarographic methods (7, 17, 19). Thus, the classical cystinuria, first described by Wolfstone in 1810, has been more accurately defined biochemically (7) and can now be distinguished easily by urine analysis from other cases with pathologically raised cystine excretion (7). Con-

siderable progress has also been made with respect to the genetics of this disease. An excellent review (5) on cystinuria, to which reference is made, covering its clinical, biochemical and genetic aspects, was recently published by Harris & Robson (12).

In the present series of papers, the term cystinuria denotes the classical cystinuria, an inherited condition involving a strong tendency to cystine calculus formation, and characterized by the excretion of *cystine, lysine, arginine* and *ornithine*. Strong evidence now supports the theory that the biochemical nature of the disorder is an impairment of the reabsorption of these four amino acids in the renal tubules (7, 15).

From the genetic point of view (12), individuals with the aforementioned condition (Phenotype I) can be regarded as homozygotes of "recessive cystinuria" or of "incompletely recessive cystinuria". In the families in which the latter variant of the disease occurs, a second type of individuals (Phenotype II) is also found. Their condition is characterized by a moderate

TABLE 1. Incidence of cystinuria as given by different authors.

Reference	Number of individuals investigated	Number of cystinurics found	Approximate incidence	Methods
Simon; Garrod, 1923 (10)	15,000	1	1 : 15,000	Microscopic examination of urine
Primavera; Garrod, 1923 (10)	20,000	1	1 : 20,000	"
Sondern, 1911 (16)	35,000	4	1 : 9,000	"
Lewis, 1932 (14)	10,534	18	1 : 600	Cyanide-nitroprusside test (Brand), Naphthoquinone sulphonie acid test (Sullivan)

excretion of *cystine* and *lysine*, a normal or only slightly elevated excretion of arginine and ornithine, and a very slight tendency to cystine calculus formation. These individuals are regarded as heterozygotes of "incompletely recessive cystinuria".

For convenience, the term *cystinuric* is used in the following to denote a person of Phenotype I; similarly, the term *incomplete cystinuric* denotes a person of Phenotype II.

No attempts have hitherto been made to estimate the incidence of cystinuria in Sweden. As will be reported elsewhere, 66 Swedish cystinurics are known to the present authors (1, 2). With few exceptions, this figure probably includes all cases of cystinuria recognized in this country since 1870, when the diagnosis was established here for the first time (9). The aforementioned figure does not, however, give any information about the real number of cystinurics existing in Sweden.

The incidence of stone formation in cystinurics is now known to be extremely high. It was recently reported (6) that, in 15 cases of cystinuria diagnosed at random, more than 50 per cent had a history of

renal lithiasis. A still higher incidence of stone formation and a definite decrease in life span in a number of male cystinurics was found in a similar study based on the Swedish material of cystinuria (2).

There are good reasons to believe that the prognosis of cystinurics with respect to the severity of stone complications, and possibly even to life span, would improve considerably if these cases were recognized earlier and, if necessary, kept under suitable control and on a stone-preventing regime (8).

The following study was undertaken with the object of obtaining some information on the incidence of cystinuria in Sweden, as well as a firmer basis for discussing the possibilities of organizing a more general "cystine stone-prevention service" in such a relatively small country.

Experimental

Case Material

All children entering the first grade of any of the Swedish elementary schools—usually at 7 years of age—have to pass a medical examination, including a test for the presence of sugars or proteins in the urine. The urine analysis is generally made

by the school nurses, who also give instructions for the collection of urine (50 ml sample of morning urine). In order to obtain an appropriate number of urine specimens taken at random for the present study, it was found convenient to base the collection of specimens on this already existing health programme of the schools. Through the courtesy of the Chief of the School Health Service in Stockholm, Dr. Urban Hjärne, and with the kind cooperation of the school nurses in all elementary schools belonging to the City of Stockholm, the following arrangement was made.

The school nurses were instructed, after testing a certain number of urines for the presence of sugars and proteins, to save the rest of the urine samples, and to report to our laboratory that specimens were available. These specimens were collected every afternoon from the relevant schools by a car sent from our laboratory. They were kept overnight in the laboratory at $+4^{\circ}\text{C}$, and the chemical analyses were started on the following morning. In a few cases the specimens were kept at room temperature in the schools for one or two days, but in all these cases a crystal of thymol was added to each flask as preservative.

In the autumn of 1957, 9534 children entered the Stockholm elementary schools; urine specimens were analyzed with respect to cystinuria in 7793 of them, i.e., 81.7 per cent. No specimens were obtained from 1741 children (18.3 per cent). This was mainly due to the outbreak of an influenza epidemic (Asian flu) during the later part of the period during which this study was undertaken (September and October), with

a high frequency of absence from school on the scheduled days of medical examination of the different classes. The missing children—who had to undergo this examination after return to school—were omitted from our study, since collection of all these specimens from many different schools would have been both difficult and expensive. Of the children investigated, 3960 (50.8 per cent) were boys, and 3534 (45.4 per cent) were girls. Due to inadequate labelling of the urine flasks, 299 children (3.8 per cent) remained "sexless".

Urine specimens were also obtained from most of the parents and sibs (55 persons) of all schoolchildren finally classified as cystinurics or incomplete cystinurics.

Methods

All specimens were tested with the cyanide-nitroprusside reaction, according to Brand (3), in the following way. To 3 ml of urine are added 2 ml of a 5 per cent sodium cyanide solution, and the reaction is allowed to proceed for about 5 minutes. A few drops of a freshly prepared 5 per cent solution of nitroprusside are then added, and thorough mixing ensured. A positive reaction is shown by the appearance of a fairly stable magenta colour. The positives were classified visually as $++++$, $+++$, $++$, $+$, $(+)$, on the basis of the colour intensity. All negatives were discarded. The positives were kept in the deep-freeze for subsequent investigation.

For further classification, amounts of urine corresponding to $15\text{ }\mu\text{g}$ of creatinine were taken from all positives for ascending paper chromatography according to Datta, Dent & Harris (4), using phenol-water (500 g phenol + 125 ml H_2O) as first solvent, and lutidine-water (200 ml lutidine + 100 ml H_2O) as second solvent. Development of the chromatograms was performed at 40°C for one hour, after spraying with 0.2 per cent ninhydrin, dissolved in butanol.

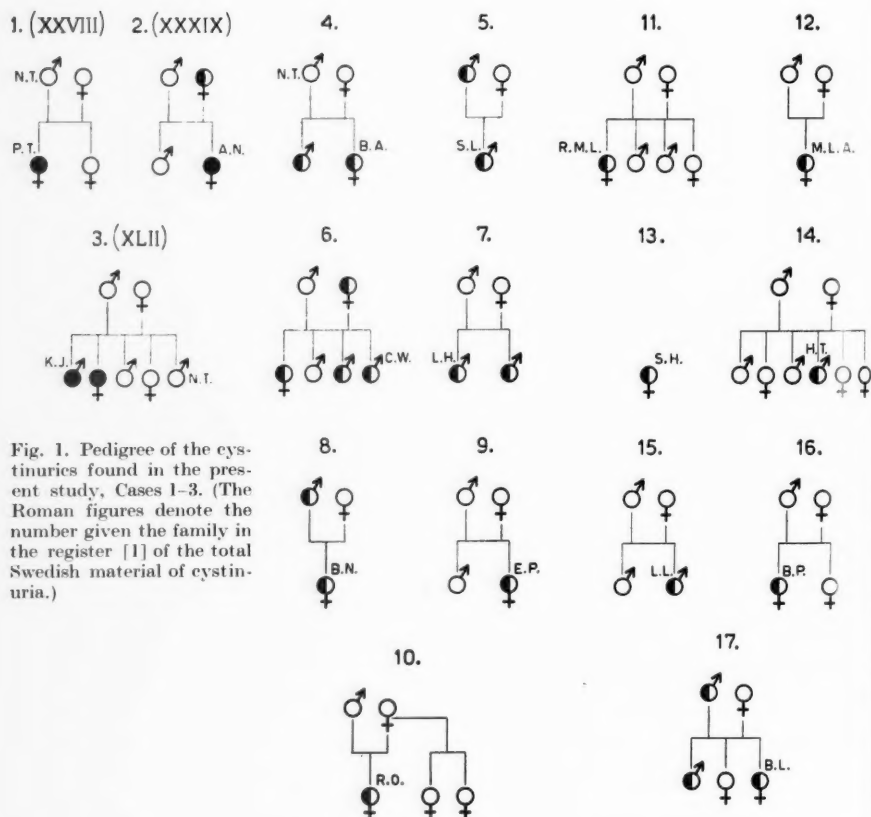
In order to differentiate between cystinurics (cystine-lysine-arginine-ornithine pattern) and incomplete cystinurics (cystine-lysine pattern), paper electrophoresis at pH 9.6 and at pH 11.0 was also done on the

TABLE 2. Sex distribution in the present material.

Sex	Number of children tested	Per cent of total number
Boy	3960	50.8
Girl	3534	45.4
Sex unknown	299	3.8
Total	7793	100

TABLE 3. Results of the laboratory findings.

Case no.	No. of cases	Cyanide-ni- troprusside test	Results of laboratory investigations					Final classification
			Paper electrophoresis			Paper chromatography		
			Arginine	Lysine	Ornithine	Lysine	Cystine	
1-3	3	+++	+++	+++	+++	+++	Cystinurias	
4-7	4	++	-	++	-	++		
9-10	2	++	-	+	-	+		
8	1	+	-	++	-	++	Incomplete cystinurias	
11-14	4	+	-	+	-	+		
15-16	2	+	-	(+)	-	(+)		
17	1	(+)	-	(+)	-	(+)	Normals	
18-23	6	(+)	-	(+)	-	(+)		
24-7793	7771	-						



Figs. 2-3. Pedigrees of the incomplete cystinurias found, Cases 4-17.

same amount of urine from all cyanide-nitroprusside positives (13).

All cystinurics found were subjected to an ordinary physical examination, and an X-ray scout film of the kidney region was taken.

Results

The results of all analyses made on the schoolchildren are summarized in Table 3. As can be seen from this table, 23 specimens were picked out of the whole material, on account of the positive or suspectedly positive cyanide-nitroprusside reaction. In three of these cases (1-3) a very strong reaction was obtained, and a typical cystine-lysine-arginine-ornithine pattern was established by paper chromatography and paper electrophoresis. These children were therefore classified as cystinurics.

In another group of 11 children (Cases 4-14), a medium or weak but definitely positive nitroprusside reaction was obtained. In all these cases a cystine-lysine pattern was easily recognized, and the children were therefore classified as incomplete cystinurics. In a third group of three children (Cases 15-17), only a weak or suspicious cyanide-nitroprusside reaction was obtained, but a definite increase in cystine excretion was demonstrated by paper chromatography. Although an increased lysine excretion was somewhat difficult to establish, these three cases were included in the group of incomplete cystinurics. In Case 17, which was most suspicious, strong evidence in favour of this diagnosis was obtained by demonstration of additional cases of incomplete cystinuria in the proband's family (Fig. 3). In the last 6 cases with a somewhat suspicious cyanide-nitroprusside reaction, no

TABLE 4. *Incidence of cystinurics found in the present study.*

Sex	Number of children tested	Number of cystinurics found	Number of incomplete cystinurics found	Total
Boys	3960	1	5	6
Girls	3534	2	9	11
Sex unknown	229	—	—	—
Total	7793	3	14	17
Incidence	—	1 : 2598	1 : 557	1 : 458

definite increase in either cystine or lysine was found by paper chromatography. These children, in addition to the 7769 children who showed a negative reaction in the Brand test, were classified as normals (Table 4).

The incidence of cystinurics in the group of children investigated in the present study was 1:2598. The corresponding incidence of incomplete cystinurics was 1:557. Finally, the incidence of children with a definitely raised urinary excretion of cystine (cystinurics + incomplete cystinurics) was found to be 1:458.

Analyses of urine specimens obtained from 10 relatives—parents and sibs—(Table 5, Fig. 1) of the three cystinurics disclosed one additional cystinuric among the sibs (Pedigree 1) and one incomplete cystinuric among the parents (Pedigree 3). In similar investigations on 45 relatives of the 14 incomplete cystinurics (Table 5, Figs. 2-3), 9 new incomplete cystinurics in 6 families (Pedigrees 4-8 and 17) were detected.

The case histories and physical examination of the three cystinuric schoolchildren were entirely negative with respect to the urinary tract. Thus, there was no history

TABLE 5. *Number and type of positives found among relatives (parents and sibs) of cystinurics and incomplete cystinurics.*

Type of proband	Number	No. of relatives (parents and sibs) investigated	No. of cystinurics found	No. of incomplete cystinurics found
Cystinuric	3	10	1	1
Incomplete cystinuric	14	45	0	9
Total	17	55	1	10

of passing of stones, renal colic or symptoms or signs of cystitis or cystopyelitis. All three children were of ordinary size and weight and looked healthy. No pathologic features referable to the urinary tract were found on physical examination, including blood pressure determination, examination of heart and lungs, and palpation of the abdomen with special reference to the kidney region. The survey X-ray of the kidney region was normal.

The fourth cystinuric traced, a younger sib of one of the probands, was also, according to a report from her mother, a perfectly healthy 5-year-old girl.

Discussion

The foregoing results are based on a screening study of 7793 schoolchildren, representing 81.7 per cent of all pupils entering the first grade of the elementary schools in Stockholm. The fact that 18.3 per cent of pupils in the age group of schoolchildren studied were excluded from this investigation, owing to absence from school on the scheduled day of medical examination, is probably of no importance for the reliability of the results. This is

because the chance that a cystinuric child would be absent from school on this particular day due to an acute manifestation of cystinuria must be considered as extremely small.

The group of individuals on which the present study is based can be regarded as a fairly representative sample, not only of the elementary schoolchildren in Stockholm (78,944 pupils in the autumn of 1957), but also of the total population of Stockholm (798,913 on Jan. 1, 1958). For, no social or racial segregation occurs in the schools, which could give rise to an undesirable selection of the basic material. Moreover, it seems likely that a reasonable correlation exists between the population of Stockholm and the average population of the whole country (7,392,872 persons on Jan. 1, 1958). This assumption is based on the great homogeneity of the Swedish population, as well as the rapid immigration to Stockholm from all parts of the country that has taken place during the present century.

The methods used in the present study have proved to be adequate for a sharp differentiation between normals and cystinurics, between cystinurics and incomplete cystinurics, and between normals and incomplete cystinurics with moderately raised cystine or lysine excretion. The problem of differentiating sharply between normals and incomplete cystinurics with very slight impairment of cystine and lysine excretion is, however, more difficult. These cases require more complicated quantitative methods, which are inconvenient to apply in screening studies (12). Consequently, it seems possible that some of the incomplete cystinurics of this type were missed in the present screening, and

the incidence given for incomplete cystinurias must therefore be considered as a minimal figure.

In view of the low number of positives found among the cystinurias, the incidence figure (1:2598) given in Table 4 must be regarded as a point estimate of the incidence of cystinuria among Stockholm schoolchildren associated with a considerable statistical error. Calculated with customary statistical methods, the confidence limits at the 95 per cent probability level were found to be 1:12,569 to 1:891. A still higher degree of uncertainty—which cannot be estimated on the basis of present knowledge—could be expected with regard to the distribution of the cystinuric gene in the population, if an attempt were made to estimate the total number of cystinurias in Sweden on the basis of the present study.

Despite these reservations, it can be presumed that the number of cystinurias living in this country is relatively high, and many times greater than the number of cystinurias hitherto detected.

It has recently been stressed that, as far as stone complications are concerned, the prognosis is poorer for cystinurias than was earlier believed. It can therefore be concluded that central registration of cystinurias in Sweden, as well as an organized stone prophylaxis, would be of considerable value.

Summary

The incidence of cystinuria has been studied by screening of urine specimens of 7793 schoolchildren from all elementary schools in Stockholm. In this material, 3 cystinurias and 14 incomplete cystinurias

were found. It is concluded that the total number of cystinurias in Sweden is relatively high, and many times greater than the number hitherto recognized. It is suggested that central registration of cystinurias and an organized stone prophylaxis would be of considerable value.

La cistinuria en Suède. II. Incidence de la cistinurie homozygote chez les écoliers suédois

L'incidence de la cistinurie a été étudiée par l'analyse d'échantillons d'urines recueillis de 7793 écoliers de toutes les écoles primaires de Stockholm. On découvrit dans ce groupe 3 cystinuriques et 14 cystinuriques incomplets. La conclusion que l'on en tire est que le nombre des cystinuriques pour l'ensemble de la population suédoise est relativement élevé et qu'il est de plusieurs fois supérieur à celui que l'on connaissait jusqu'ici. L'auteur pense que l'établissement d'un fichier central des cystinuriques et une prophylaxie organisée des lithiases seraient extrêmement utiles.

Zystinurie in Schweden. II. Das Vorkommen von homozygotischer Zystinurie bei schwedischen Schulkindern.

Das Vorkommen von Zystinurie bei Schulkindern wurde studiert, indem der Harn von 7793 Kindern aus allen Elementarschulen in Stockholm einer Routineuntersuchung unterzogen wurde. Unter dem untersuchten Material fanden sich 3 Fälle mit kompletter und 14 mit nicht kompletter Zystinurie vor. Es wird der Schluss gezogen, dass die Gesamtzahl der Zystinuriefälle in Schweden relativ hoch und vielmal grösser als bisher angenommen wurde, sei. Die Verfasser sprechen die Ansicht aus, dass eine zentrale Registrierung der Zystinuriefälle und organisierte Harnsteinvorbeugung von beträchtlichem Wert sein würde.

La cistinuria en Suecia. II. Incidencia de la cistinuria homocigótica en los escolares suecos

La incidencia de la cistinuria ha sido estudiada mediante el examen de muestras de orina de 7.793 escolares de todas las escuelas elementales de Estocolmo. En este material se hallaron 3 pacientes cistinúricos, y otros 14 con cistinuria incompleta. Se concluye en que la cifra total de cistinúricos en Suecia es relativamente elevada, y muy superior a la cifra admitida hasta ahora. Se sugiere que el registro central de los cistinúricos, y la profilaxis organizada de los cálculos tendrían gran utilidad.

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Dept. of Metabolic Research
Wenner-Gren Institute
Stockholm, Sweden

Coarctation of the Aorta

A Postoperative Functional Study

by DANAE IKKOS, GÖRAN WALLGREN and PER ZETTERQVIST

Since the introduction in the mid-forties of surgical techniques for the correction of coarctation of the aorta, a number of investigations concerning the results of such correction have appeared (9, 14). For the most part, these studies have dealt with the influence of the operation upon the resting blood pressure in the upper part of the body, at various intervals after operation (1, 5, 6, 7, 8, 10, 11, 13, 19, 21). Normalization of this pressure has been considered to indicate a good result of the operation, and on the basis of this criterion, good results have been found in 50–75 per cent of the operated cases.

In order to get information about the remaining degree of stenosis after operation, some investigators have studied simultaneously recorded pressure curves from the brachial and femoral arteries. This procedure permits the use of the ratio between the systolic pressures as well as the time-lag between the pulses in the arteries, as information reflecting the remaining functional stenosis in the anastomosis. These investigators have found, that in spite of a normalization of the blood pressure in the upper part of the

body, there have very often been signs of a residual stenosis (4, 11, 12, 15, 19, 23, 25).

The above-mentioned studies have all been dealing with the influence of the operation upon the hemodynamics at rest. It has occurred to us, that the study of hemodynamics during work might present a more sensitive method to appraise the functional state of the cardiovascular system after operation. The augmented requirements put upon the circulation during exercise should increase or even provoke signs of functional incapacity.

Material

Fourteen patients, who had been operated upon for coarctation of the aorta 2 to 7 years previously, were studied. The sex of the patients as well as the age at operation and at the time of the present investigation are listed in Table 1. Four of the patients had a small associated patent ductus arteriosus, which was ligated at operation (Cases 4, 8, 9 and 12). One patient (Case 14) had an associated valvular aortic stenosis of a slight degree, and another (Case 2) had a mitral stenosis with atrial fibrillation. No attempts to repair these valvular defects were made at time of surgery. The remaining 8 cases were all typical cases of isolated coarctation.

TABLE 1 A. *Operated coarctations.*

Case no.	Sex	Age in years		Working capacity per cent of normal average	Systolic arm blood pressure mm Hg	
		at op.	actual		rest	work
1.	M	11	14	77	155	200
2.	M	12	15	74	120	150
3.	F	8	10	91	150	190
4.	M	8	15	100	130	175
5.	F	8	11	68	175	275
6.	M	6	12	80	145	215
7.	M	9	13	73	155	215
8.	M	12	14	109	130	175
9.	M	4	8	71	130	150
10.	M	9	13	75	130	190
11.	F	16	21	60	130	190
12.	M	11	15	104	150	195
13.	M	17	20	100	120	170
14.	M	9	15	98	135	210
		Mean	12.9 \pm 0.6	85 \pm 4.2	142 \pm 9.7	195 \pm 9.5

Essential data concerning the 14 operated cases.

All patients were free of symptoms of functional incapacity, and all of them were admitted to the Clinic only for the purpose of the present follow-up study. In each case a routine examination was made, including ECG, PhCG and roentgenography of the heart.

As a control material we have investigated 17 normal children of corresponding age, regarding their working capacity as well as their arm blood pressure at rest and during submaximal work.

Methods

The exercise test was first performed in sitting position on a bicycle ergometer (22, 24). The 'submaximal working capacity' was estimated, defined as the load in kgm per minute corresponding to a pulse rate of 170 beats per minute. Blood pressure measurements were made with an air manometer before and every two minutes during the exercise. The values given in this article for pressure measurements at work are those obtained at a pulse rate of 170 per minute.

On the following day the exercise was repeated in the recumbent position. During this second test, intra-arterial blood pressure measurements were made simultaneously from the right brachial artery and the left femoral artery by means of two strain-gauge manometers (ELEMA). An indwelling needle was used for the brachial artery, while a polyethylene catheter was inserted into the femoral artery (20). Blood pressures were registered immediately after the puncture and later when the patient was in a quiet state. Two six-minute-periods of work were performed by each patient, the first one with a load corresponding to half the submaximal working capacity found the previous day, and the second with approximately the total one. Blood pressures were recorded at the end of the first, third, and sixth minute of each period.

Results

Working capacity: The results of the exercise test on the bicycle ergometer are listed in Table 1. The working capacity

TABLE 1 B. *Normals.*

Case no.	Sex	Age years	Working capacity per cent of normal average	Systolic arm blood pressure mm Hg	
				rest	work
1.	M	15	85	130	185
2.	M	14	93	115	180
3.	F	15	79	115	175
4.	M	14	119	120	170
5.	M	14	96	130	160
6.	F	11	83	130	160
7.	F	14	78	130	155
8.	F	15	94	120	155
9.	F	16	75	115	155
10.	F	14	75	110	150
11.	F	14	94	120	120
12.	M	8	88	110	150
13.	M	11	92	120	135
14.	F	11	147	100	130
15.	M	11	97	105	130
16.	F	11	70	115	125
17.	M	12	112	110	125

Mean 13.0 ± 0.5 92 ± 4.6 117 ± 2.2 152 ± 4.5

Essential data concerning the 17 normal cases.

of each child is expressed in per cent of the normal mean value for the actual body weight given in the literature. The average submaximal working capacity values of the two groups did not differ significantly from each other ($p > 0.05$).¹

Blood pressure in the arm: The individual figures for the blood pressure in the right arm measured by air manometer, at rest and during work for both groups, are also listed in Table 1. The mean values for the coarctation group are significantly higher ($p < 0.001$) than those of the control group both at rest and during work. The mean rise in the systolic blood pressure during work was somewhat higher in the coarctation group, but the difference is not significant.

¹ In order to get the two groups comparable as regards age, the two oldest patients were excluded in calculation of the mean values for the coarctation group.

TABLE 2.

Case no.	Blood pressure brachial artery mm Hg				Blood pressure femoral artery mm Hg				Pressure gradient between brachial and femoral artery	
	rest		work		rest		work		rest	work
	S. ¹	D. ²	S.	D.	S.	D.	S.	D.		
1.	135	87	210	110	—	—	—	—	—	—
2.	140	86	130	90	—	—	—	—	—	—
3.	163	87	205	66	121	81	111	89	42	94
4.	116	60	180	80	100	63	100	75	15	80
5.	150	87	180	95	112	85	100	82	38	80
6.	142	80	178	79	124	74	110	75	18	68
7.	115	60	175	78	113	76	128	89	2	47
8.	140	93	168	120	135	82	160	100	5	8
9.	130	70	160	75	130	74	120	93	0	40
10.	125	72	160	72	145	87	148	87	-20	12
11.	125	72	164	98	125	76	134	93	0	30
12.	145	90	195	95	112	86	120	100	33	75
13.	130	86	180	110	140	94	150	110	-10	30
14.	130	75	160	87	120	75	140	100	0	20
Mean	134	80	175	90	123	79	126	91	10.3	48.7
S. error	± 3.7	± 2.8	± 5.5	± 4.3	± 3.7	± 2.5	± 5.7	± 3.1	± 5.6	± 8.6

¹ S = Systolic. ² D = Diastol.

Intra-arterial pressure recordings in the 14 operated cases.

Intra-arterial pressures: The intra-arterial pressures in the brachial and femoral arteries at rest and during work are listed in Table 2, as are the pressure gradients in systole between the two vessels at rest and during work. The average systolic increase in the brachial artery during work did not significantly differ from that found by the cuff method with patients in the sitting position. No attempts were made to correlate the absolute values obtained by the two methods, as the two investigations were made under different circumstances.

The average systolic pressure in the femoral artery did not change from rest to work. However, the individual variations are of some interest, as there is a slight tendency to a decrease during work in those cases having a definite positive pressure gradient at rest. In the remaining cases an increase is generally found.

The average diastolic pressure is approximately the same in the two arteries both at rest and during work, and an increase of about 10 mm Hg is noted during work.

Pressure gradient: A pronounced positive systolic pressure gradient between the brachial and femoral arteries was present in five out of twelve patients (Cases 3, 4, 5, 6, 12), while in the remaining cases there existed no gradient or even a slightly negative one. During work, however, a positive systolic gradient was found in all cases except one (Case 8), the mean value for the gradients at rest and during work being 10.3 ± 5.6 and 48.7 ± 8.6 respectively.

Correlation of intraarterial arm blood pressure to gradient: The degree of statisti-

TABLE 3.

	S. B. P. at work	Gradient at rest	Gradient at work
S. B. P. at rest	0.355*	0.741**	0.508†
S. B. P. at work	—	0.794**	0.811**
Gradient at rest	—	—	0.871***

Intercorrelation of systolic blood pressure (S. B. P.) in the brachial artery and the systolic pressure gradient between brachial and femoral arteries at rest and during work.

Symbols stand for: * $p > 0.05$, ** $p < 0.01$, and *** $p < 0.001$ respectively.

cal significance of the intercorrelations between systolic arm blood pressures and gradients, at rest and on effort, is listed in Table 3. It is striking, that the blood pressure at rest shows no correlation to either pressure or gradient at work.

Discussion

The finding that all the patients were completely free from symptoms referable to the circulatory system, as well as the fact that their working capacity was not less than that of the control group, is not surprising, as it is well known that young patients with coarctation of the aorta, even before operation, usually have no or very mild symptoms and may sometimes be capable of performing very heavy work (18).

The average systolic blood pressure in the upper part of the body, measured by the air manometer, at rest as well as during work, was significantly higher in the operated cases than in the control group. Our findings as regards the systolic blood pressure at rest are in agreement with those of previous authors (1, 6, 8, 11, 13,

19, 21, 25). Definite increase of this pressure was observed in 6 out of the studied 14 cases (Cases 1, 3, 5, 6, 7 and 12), and in an additional 6 cases it was elevated above the normal average.

It might be questioned whether the emotional situation was similar in the two groups. Major influence, however, of this on the blood pressure could be excluded as the average pulse rate at the time of measurement did not differ between the two groups.

Also the time factor is to be taken into consideration in judging the blood pressure values. It is well known, that a certain time must elapse after operation of coarctation, before there is a stabilization of the hemodynamic changes, and the pressure may rise or fall during fairly long periods (5, 15, 16, 19, 23, 25). In our material the observation time is only in one case (No. 8) somewhat less than two years (18 months), and in the other cases it is at least two years, a period after which we suppose hemodynamics to have been stabilized.

Looking at Table 2 we find that all cases, except No. 8, have shown a positive gradient at work regardless of their arm blood pressure at rest. Even in those cases, where a negative gradient was obtained at rest, a positive one appeared during exercise.

Of special interest are the findings in Cases 7, 9, 11, 13 and 14. In these cases neither the values for the intraarterial systolic pressure in the brachial artery at rest nor the pressure gradient values at rest show evidence of a residual stenosis. During work, however, all five patients present positive gradients of 47, 40, 30, 30 and 20 mm Hg respectively. As it has been shown by others (17), that during

moderate work in normal adults only minor gradients between arm and leg may be expected, we have considered it permissible to judge a gradient of 20 mm Hg or more to be of significance.

Contrary to the systolic pressure conditions, the diastolic pressure in the leg in most cases is not lowered compared to that of the arm. This, of course, has a beneficial effect upon the effective circulatory pressure in the lower part of the body.

Somewhat surprising are the findings in case No. 8, where an elevation of the diastolic pressure is found in both arm and leg, and where the absence of a systolic gradient excludes the presence of a major residual stenosis. The elevated diastolic pressure indicates an increase in the peripheral resistance. We are, however, not readily inclined to judge this case as a truly hypertensive one, as the observation time is the shortest in our material and the hemodynamics might not yet have been stabilized. A follow-up study in this case is certainly warranted.

In the other cases the hypertension is limited to systole and to the upper part of the body. The normal diastolic pressure values practically exclude an increase in the peripheral resistance as a cause of the hypertension, and the pressure gradient between arm and leg—exaggerated or provoked by the increased flow during physical work—strongly suggests the existence of a residual stenosis.

If the presence of a positive systolic gradient between arm and leg during exercise is accepted as evidence of a residual stenosis at the site of the anastomosis, such a stenosis was found in 10 out of 12 cases studied by intra-arterial pressure measurements. This finding is in

agreement with the results of Brodén & Karnell (3), who found by postoperative aortography in 105 patients a residual stenosis of varying degree in approximately 75 %. Thus the present study seems to indicate that evaluation of the hemodynamic conditions during exercise would be a more sensitive and accurate method in appreciating the postoperative results in coarctation of the aorta than would

measurements during rest only. Further studies with comparison of the functional and anatomical conditions of anastomosis are in progress.

Even if the hemodynamics postoperatively are thus not completely normalized, the beneficial effect of the operation in arresting the progressive disabling course of the disease should be fully understood and appreciated.

Summary

Measurements of the systolic pressure in the arm as well as the systolic pressure gradient between the brachial and femoral arteries were performed at rest and during work in 14 patients operated 18 months-7 years previously for coarctation of the aorta.

The average systolic blood pressure in the arm was higher in the coarctation group than in a control group both at rest and during work. Intraarterial measurements at rest in the coarctation group showed a systolic pressure gradient between the brachial and femoral arteries

of more than 20 mm Hg in 5 out of 12 cases. During work a pressure gradient of more than 20 mm Hg appeared in 10 of the 12 cases. The average value of the gradient for the 12 patients was at rest 10.3 ± 5.6 mm Hg and during work 48.7 ± 8.6 mm Hg.

In 5 of the cases a pressure gradient appeared during exercise, although both systolic pressure and gradient were within normal limits at rest. Thus hemodynamic studies during exercise would seem to be a sensitive test in evaluating operative results in coarctation of the aorta.

Coarctation de l'aorte. Étude fonctionnelle post-opératoire

Des mesures de la pression artérielle systolique au niveau du bras et du gradient de pression systolique entre les artères fémorale et brachiale, ont été faites au repos et lors du travail, chez 14 patients avec coarctation de l'aorte, opérés depuis 18 mois à 7 ans. La valeur moyenne des pressions systoliques au niveau du bras chez les patients avec coarctation est plus élevée que chez les sujets normaux témoins, tant au repos qu'au cours du travail. La mesure des pressions artérielles au repos chez les patients avec coarctation montre un gradient de pression, entre artère fémorale et artère brachiale, supérieur à 20 mm Hg. dans cinq cas sur douze. Au cours du travail, le gradient de pression dépasse 20 mm Hg. dans dix cas sur douze. Chez ces douze patients, la valeur moyenne du gradient atteint

$10,3 \pm 5,6$ mm Hg. au repos et $48,7 \pm 8,6$ mm Hg. lors du travail. Dans cinq cas le gradient de pression n'apparaît que pendant le travail: au repos, pressions systoliques et gradient de pression entre artère brachiale et artère fémorale sont dans les limites de la normale. En conclusion: des études hémodynamiques au cours du travail pourraient constituer un test destiné à évaluer les résultats post-opératoires chez les patients avec coarctation de l'aorte.

Coarctatio aortae. Eine postoperative funktionelle Untersuchung

Bestimmungen des systolischen Druckes des Armes sowie des systolischen Druckgradienten zwischen Arteria brachialis und femoralis wurden ausgeführt in Ruhe und während Arbeit bei 14 Patienten die 18 Monate — 7 Jahre zuvor wegen einer Coarctatio aortae operiert wurden. Der mitt-

ler systolische Blutdruck im Arm war bei der Gruppe mit Coarctatio höher als bei der Kontrollgruppe sowohl in Ruhe wie während Arbeit. Intraarterielle Bestimmungen bei der Coarctatio-Gruppe in Ruhe zeigten einen systolischen Druckgradienten zwischen der A. brachialis und femoralis von mehr als 20 mm Hg in 5 von 12 Fällen. Während Arbeit betrug der Druckgradient in 10 von 12 Fällen mehr als 20 mm Hg. Der Mittelwert des Gradienten von 12 Patienten war in Ruhe $10,3 \pm 5,6$ mm Hg. und während Arbeit $48,7 \pm 8,6$ mm Hg. In 5 der Fälle trat ein Druckgradient während der Arbeit auf, obgleich sowohl systolischer Druck wie Druckgradient in Ruhe in normalen Grenzen war. Hämodynamische Studien während Arbeit scheinen deshalb ein empfindlicher Test bei der Beurteilung operativer Resultate der Coarctatio aortae zu sein.

Coarctación de la Aorta. Estudio funcional postoperatorio

La medida de la presión sistólica en el brazo, así como el gradiente de la presión sistólica entre las arterias humeral y femoral, fué deter-

minado, en reposo y durante el ejercicio, en 14 pacientes de coartación aórtica operados de 17 meses a 7 años antes de este estudio. La presión sistólica media en el miembro superior fué más elevada en el grupo de las coartaciones que en el grupo de control, tanto en reposo como durante el ejercicio. Las determinaciones intraarteriales durante el reposo, en el grupo de las coartaciones, mostraron un gradiente de más de 20 mm Hg entre la arteria humeral y la arteria femoral, en 5 de los 12 casos así estudiados. Durante el ejercicio este gradiente de más de 20 mm Hg fué hallado en 10 de dichos 12 casos. El valor medio del gradiente para estos 12 pacientes fué en reposo de $10,3 \pm 5,6$ mm Hg y durante el ejercicio de $48,7 \pm 8,6$ mm Hg. En 5 de los casos un gradiente de presión apareció durante el ejercicio aun cuando ambos valores, presión y gradiente, se mostraron dentro de límites normales en reposo. De acuerdo a estos hallazgos, el estudio hemodinámico durante el ejercicio parece ser un método sensible en la valoración de los resultados operatorios en la coartación de la aorta.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

From the Paediatric Clinic (Sv. Heinild, M.D.), the Out-patient Department for Light Therapy (E. Reklung, M.D.), and the X-ray Department (B. Worning, D.Sc., M.D.), Finsen Institute, Copenhagen, Denmark

A Psychosomatic Approach to Recurrent Abdominal Pain in Childhood

With Particular Reference to the X-ray Appearances of the Stomach

by SV. HEINILD, E. MALVER, G. ROELSGAARD and B. WORNING

Introduction

Recurrent abdominal pain is one of the most commonly encountered symptoms in childhood, in paediatric practice as well as in paediatric and surgical wards to which children often are admitted for observation. In this presentation, recurrent abdominal pain will refer only to cases in which other demonstrable and pertinent organic causative factors have been ruled out, such as congenital malformations, intussusception, hernias, malrotation, appendicitis, genito-urinary tract disorders, tuberculous mesenteric lymphadenitis, tumours, and other more rare organic disorders. Naturally this group also includes the more readily detected alimentary cases in which the abdominal pain is referable to an over-filled gastro-intestinal tract, possibly with improper food. A group remains in which routine clinical tests will fail to disclose any abnormality, and no organic lesions will be revealed by continued observation. However, such cases are not interpreted, at least in our country, simply as psychogenic, i.e. a form of

spastic phenomena caused by central stimulation (Cushing). It is still debatable whether more refined diagnostic techniques may eventually assign the majority of such cases to the "organic group". This suggestion cannot be wholly ignored, although we hold it to be fundamentally wrong, as will be further stressed in our discussion. This group of patients is the object of our present study.

The complete clinical examination includes a psycho-social history, and also in a series of patients X-ray examination of the stomach and duodenum. The object of examining the stomach is twofold: It is generally accepted, at least since Beaumont and Pavlov's investigations, that the gastric motility and secretion are affected by psychic influence, and the senior author (Sv. H.) has made the accidental observation that some patients suffering from severe maladjustment and abdominal colic also exhibited X-ray manifestations of gastric hypersecretion. We fully agree that it would be just as reasonable to select any other region of the alimentary tract,

especially the passage through the small intestine or the colon. It is well known that earlier authors have held similar ideas.

Previous Investigations

A general review of the very comprehensive literature on abdominal pain in children showed that previous investigations could be roughly divided into four main groups:

- (1) Investigations into gastric ulcer and its genesis.
- (2) Investigations into more or less rare abnormalities, often of congenital nature.
- (3) Investigations into non-specific mesenteric lymphadenitis.
- (4) After the above three groups have been classified, there remains an abundance of publications dealing with recurrent abdominal colic, apparently without demonstrable organic cause.

This seems to make up a nosographic entity first described by Moro in a classic paper from 1913. As so often with "first descriptions", posterity does not appear to have much to add to the clinical picture. On the basis of 18 cases Moro gave a very clear description of the frequently severe, apparently spastic attacks of pain, lasting from minutes up to hours. Three of the 18 patients had so-called acetonaemic vomiting. The condition was most commonly encountered in the age range 5-7 years, the extreme limits being at 4 and 14 years. The temperature was often about 38°C, never very high. Some patients had operations because of suspected, so-called chronic appendicitis, but as rule the appendix proved to be normal. To speak of tuberculous mesenteric lymphadenitis was "utterly unfounded" in Moro's opinion, and that was as early as 1913! The children were said to be of "neuropathic constitution", a term which appears to correspond fairly well to what we now call nervous, possibly neurotic and maladjusted children. The condition was said to co-exist quite often with migraine, asthma, and enuresis as well as "vasomotor distur-

ances". Stating that the treatment ought to be symptomatic and that the prognosis was favourable, Moro concluded his paper by referring to "einen im wesentlichen psychogen bedingten Zustand". Thirty years later, Andersen & Dalggaard (1943) contributed in large measure to lending this picture a wider perspective. Having investigated a number of children with recurrent abdominal pain, they added that the cause appeared to be maladjustment at school, at home, among fellow pupils and playmates, etc. "The symptoms are somatic manifestations of the patient's psychopathological reaction to personal difficulties."

These authors found no demonstrable organic changes on X-ray films of the stomach. The symptoms disappeared after changing the environment (e.g. admission to hospital) or after instructive talks with the parents.

Schäfer, Lassrich & Wallis (1956) further extended our knowledge of this classic syndrome, setting up the following graph (Fig. 1) which clearly shows that "unlocalized pain", meaning diffuse pain in the umbilical area, gradually decreases in frequency as time goes on in order to be replaced by "localized abdominal pain". These authors are of the opinion that recurrent abdominal pain is a syndrome of multiple aetiology, but that *it manifests a manner of reaction characteristic of a given age range.*

Comparatively few studies have been concerned with X-raying the stomach and duodenum in this condition, especially for the purpose of proving or disproving the diagnosis of gastric ulcer. It appears to be frequently overlooked that in childhood the motility of the stomach is different from that in adults, the emptying being considerably more rapid (Buchheim, 1923). From among all children who were sent for consultation because of abdominal pain, Nitsch selected 50 cases, ranging in age from 6-13 years, who presented clinical symptoms which might indicate gastric ulcer. X-raying their stomachs, he found normal appearances in 26%, prepyloric ulcer in one case (2%), motility changes or gastroduodenitis in 2%, whereas the remaining 10% exhibited other

Fig. 1

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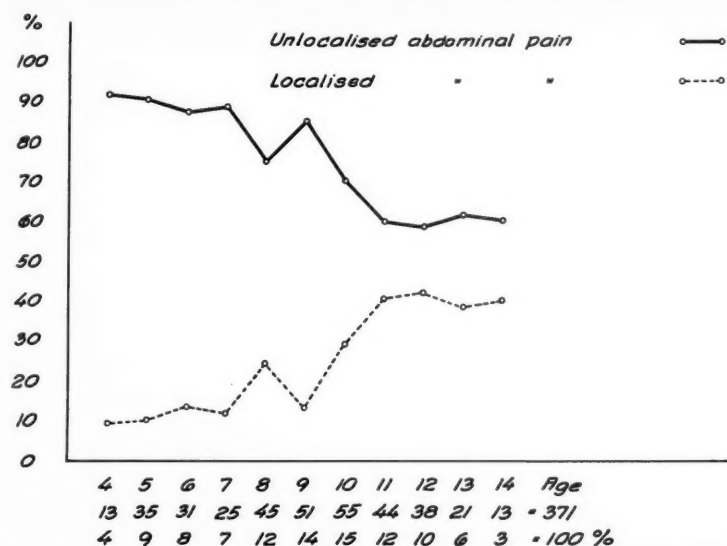


Fig. 1. Frequency of localized and unlocalized abdominal pain in 371 children ranging in age from 4 to 14 years. (After Schäfer, Lassrich & Wallis.)

lesions, such as cardiospasm, oesophagitis, or postoperative adhesions. This series was later extended to include 100 cases, but without essential alterations of the values.

X-raying the stomach, small intestine, and colon of children with recurrent abdominal pain, Giethmüller found gastritis, gastro-duodenitis, and ileitis in some (exact number not stated). It struck him that functional changes with regard to tonus, motility, and passage were *not* more common in the presence than in the absence of organic changes.

In general, X-ray examination of the stomach in children, even children with clinical dyspepsia, is stated to be unreliable for demonstrating gastritis. It is generally agreed that gastric ulcer demonstrable by X-rays only occurs in 1-2% of the 2-10-year age range.

Present Investigations

Material and Technique

The Paediatric Clinic of the Finsen Institute is an Out-patient Clinic for children referred

by general practitioners for further examination and possibly ambulant light therapy, or for admission to the associated sea-side hospital for delicate children (Kysthospitalet, Refsnæs). These patients are suffering from various forms of upper respiratory tract infections, e.g. streptococcal infections, sinusitis, and bronchitis and partly from more or less severe behaviour disorders. In addition, there are patients who are recuperating from some organic disease. In a previous paper (Sv. H.) it was demonstrated that about 60% of these patients exhibit more or less pronounced neurotic disturbances, a large proportion being severe. Recurrent abdominal pain is a common symptom among these patients, as will be seen from Table 1. In other words, *recurrent abdominal pain may be expected in about 20% of this clientele.*

The material to be presented here comprises 135 consecutive patients seen in 1949. At the end of 3 years, in 1952, they were asked to appear for follow-up. A total of 81 came, and this is the group which was analyzed. A control series is furnished by 34

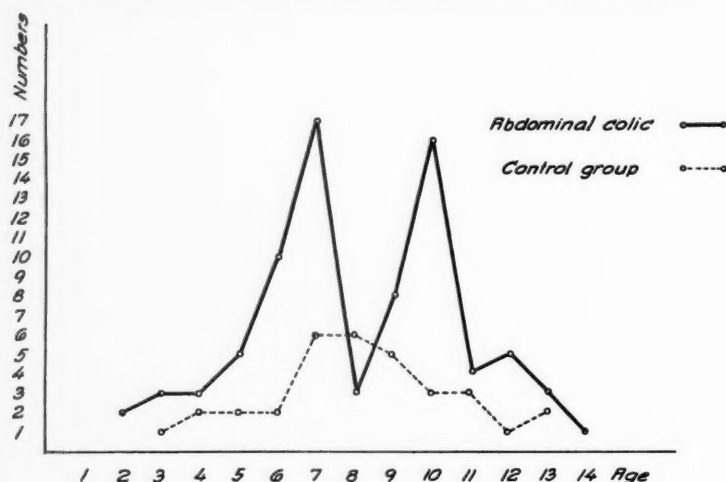


Fig. 2. Age distribution of patients and controls.

TABLE 1.

Year	No. of pats referred	No. of pats. with recurrent abd. pain	% of referred pats.
1949	1736	308	17.7
1950	2067	396	19.1
1951	2294	431	18.7
1952	2010	372	18.5
1953	1908	387	20.3
1954	1920	399	20.7
1955	1467	346	23.5

patients who had never complained of abdominal pain at any time. The findings were recorded with the assistance of laboratory, radiological, otological, and psychological experts, including parent interviews for elucidating the psychosocial aspect. When first seen, all the patients had had Ewald's test meal. As gastric function, and thus also the X-ray findings, might be imagined to be affected by the X-ray examination, i.e. the darkness during screening, the large apparatuses, and the not particularly palatable barium, it was endeavoured to carry out the examination as considerably as possible.

Most of the children did not display much fear, so the examinations could be accomplished without difficulties.

Screening was done in the supine and prone positions as well as in the erect position, supplemented by 8 special views of the prepyloric portion, the pylorus and duodenal cap. The films were read without any knowledge of the case records and by the same radiologist (B. Worning).

The term "infectious states" comprises mainly the various forms of upper respiratory tract infections which occur in childhood, including tonsillitis, sinusitis, and bronchitis. In addition, there was a certain number of streptococcal, a few staphy-

TABLE 2. Sex distribution of patients and controls.

	Boys	Girls
Patients with recurrent abdominal colics (81)	58 %	4 %
Controls (34)	67.7 %	3.3 %

TABLE 3.

Diagnosis	Patients with abd. colic		Controls	
	No.	%	No.	%
Pure infectious state	7	8.6	10	29.4
Infectious state + maladjustment	47	58.0	18	52.9
Total no. of pats. with infection	54	66.7	18	85.2
Pure maladjustment	24	29.6	4	11.8
Total no. of pats. with maladjustment	71	87.7	22	64.1
Indeterminable	3	3.7	2	5.9

loecoccal infections, and a few cases of fever of unknown cause. On the other hand, there was no instance of tuberculosis.

The diagnosis of maladjustment covers a rich selection of the psychopathological reactions seen in childhood, ranging from unrest and restlessness, through defiance and jealousy reactions, enuresis, tics, eating problems, school problems, to real anxiety and compulsion neuroses. As presumed aetiological factors we found disharmonious homes, divorces, single mothers with outside jobs, poor housing, poor economy, authoritarian or insufficient methods of upbringing. As might be expected, due to the criteria of selection, the percentage of infections was somewhat higher in the control series than in the actual series in which maladjustment predominated, but it will be seen that the difference was not particularly marked. In our experience, as was stressed in the above-mentioned previous paper (9), in childhood it is very often not a question of either infection or maladjustment, but of both. As far as we can see, this must involve a wide perspective as regards the occurrence of psychosomatic diseases which will not, however, be discussed further in this connection.

As mentioned above, X-ray examinations of the stomach and duodenum were made in all patients and all controls, in the former when first seen and again 3 years later, and in the latter only when first seen.

X-ray examination of the stomachs of children with clinical gastric symptoms usually revealed only motility and mucosal changes. *A priori*, therefore, this systematic X-ray investigation was not expected to reveal major organic changes, so in reading the films, pains were taken to record any divergence from the entirely normal X-ray appearances.

The following changes were observed: increased peristalsis, coarse, irregular mucosal folds in the body of the stomach and/or the prepyloric portion and/or the duodenal cap, divided into changes of mild, moderate, and severe degree. Only one case exhibited a gastric ulcer, with a crater in the duodenal cap.

Out of the 81 patients with abdominal colic, 65 or 80% had one or more of the

TABLE 4.

X-ray findings	Pats. with recurrent abd. colic		Control group	
	No.	%	No.	%
Increased peristalsis	9	11	0	0
Coarse, irregular or blurred mucosal folds in the body, prepyloric part, or duodenal cap				
Mild	40	49	7	21
Moderate	9	11	0	0
Severe	7	9	0	0
Total abnormal findings	65	80	7	21
Increased peristalsis plus mucosal changes	38	47	1	3
Hypersecretion	33	41	18	53

above-mentioned changes. The corresponding values for the control series were 21% out of 34 patients. Table 4 sets out the findings.

This mode of analysing the material clearly brings out the differences between the two series. Except for one case among the controls, increased peristalsis occurred exclusively in the patients with abdominal pain. Mucosal changes were 4 times as common and somewhat more severe in the abdominal cases than in the control group, and in the latter they were invariably mild. In the colic group the mucosal changes involved the body of the stomach in one case, the prepyloric portion in 2, the duodenal cap in 24, the prepyloric portion + duodenal cap in 27, the body + prepyloric portion + duodenal cap in 2. In the controls, these changes affected only the duodenal cap in 3 cases, whereas in the remaining 4 they involved the prepyloric portion as well as the duodenal cap. In the patients with abdominal pain the mucosal changes were usually associated with increased peristalsis (in 38 or 47%).

Table 4 reveals that 33 of the children with colic had hypersecretion. This corresponds to 41% as compared with 18 out of 34 controls or 53%. In this connection, it should be mentioned that only two of the abdominal cases had increased acidity according to the criteria of Behrendt. Both failed to show any abnormalities in the two X-ray examinations. Twenty patients yielded more than 200 ml at Ewald's test meal, but only 9 of these exhibited X-ray signs of hypersecretion.

This would appear to disprove one of the working hypotheses which formed the basis of the present investigation; namely the demonstration of gastric hypersecre-

tion in maladjusted children with recurrent abdominal pain.

Follow-up

The mucosal changes found on the first examination were still present 3 years later in 75% of the patients and increased peristalsis in 68%. Another most important finding was that *these changes were not present as a new phenomenon at follow-up*, except in two patients who originally had mucosal changes and at follow-up also had developed increased peristalsis. The patient who had ulcer when first seen still had it 3 years later.

In accordance with what has been stated above, hypersecretion appeared more accidentally distributed at follow-up, being still present in 45% and appearing as a new phenomenon in 27%.

It may be added that the mucosal changes at follow-up showed some variation in severity, 15 cases showing radiological improvement, 8 exacerbation, while 19 were unchanged. This agrees with the fact that at the time of the first examination the mucosal changes were associated, in two-thirds of the cases, with increased peristalsis, while at follow-up this co-existence was seen in only about half the patients.

No definite correlation was found between the X-ray findings and the subjective complaints at follow-up, the colic having been reduced and perhaps had disappeared regardless of the X-ray findings. The absolute values representing the clinical condition at follow-up are given below.

No. of pats.	Colic unchanged	Colic improved	Symptom- free	No. lin- follow-up
81	5	28	36	1

A comparison of the results of clinical follow-up, i.e. improvement or complete subsidence of abdominal colics within 3 years in at least two-thirds of the patients, with the fact that X-ray abnormalities were still present in almost 75 %, goes to confirm the fact that the symptom of recurrent abdominal colic gradually decreases with the passing years. *The X-ray signs subside more slowly than the subjective complaints, if they ever subside*, but this is a question which cannot be solved by the present study.

Treatment consisted, in practically all cases, of one or more series of light baths. In addition, 7.4 % of the patients spent 3-4 months in coastal climate at the Refsnæs Hospital. In all cases, the parents were called in for educational conversations, but actual classic psychotherapy was not employed. Medication was not prescribed in any case, nor bed rest, especially during the stay at the Coast Hospital—except for children with intercurrent, febrile diseases.

Discussion

The present material deals with the syndrome generally named recurrent abdominal colic of psychogenic origin. It comprises a group of patients from which every case with a reasonable "organic" aetiology has been eliminated. This study reveals two important features, namely that *about 90 % of the cases exhibit evident maladjustment, and that infection does not appear to be a predisposing factor* as is often claimed.

In our opinion, however, the term psychogenic abdominal pain is a misnomer. It is destined to misdirect further investigations and serves to maintain the

unfortunate modern trend to discriminate between "real" organic diseases and the group which should solely be designated as of "psychogenic", nervous, functional causation, or whatever term is used. Our investigation reveals that when a limited organic area is selected from such a "psychogenic" material, as for example the stomach—which in fact did attract attention due to regional pain—such an organic area does not remain passive. On the contrary, about two-thirds of all cases exhibited X-ray changes in the form of increased peristalsis and alterations of the mucosal pattern. These changes were of such tangible character that they were still present at follow-up 3 years later in about three-quarters of the cases—even though the pain had almost subsided at that time. However, it seems clear that it would be artificial, on the one hand, to distinguish between the single case of ulcer disclosed in our series and, on the other hand, the 80 cases without the classic X-ray signs of ulcer, especially after Alvarez' finding that the symptoms may be exactly the same whether or not an ulcer is present (see also Davies & Wilson).

We feel, therefore, that our study might modestly contribute to re-establish the biological concept which looks upon the human body as an entity, and not solely as a collection of organs functioning with varying success.

We would like to warn against a tendency in a number of otherwise excellent studies on related problems, not least within gastroenterology, which is best characterized by a couple of verbatim quotations: "Many of these patients are classified as nervous" or "this pain is deemed nervous by the doctors, until finally an X-ray examination is done,

and an ulcer is disclosed as the underlying cause of the complaints".

Such and sundry similar statements seem to overlook that the origin of any pathological condition, except for traumatic injuries, must be of functional nature, whatever elicited the disturbance of function. Even a massive organic abnormality must originally have started with subclinical changes.

Because of the uncertainty which still prevails about radiology of the stomach in childhood, it is difficult to assess the significance of the X-ray changes found in the present study. It may be said, however, that children with a short or long history of abdominal colic exhibit a state of gastric irritation more often than children without this symptom. This state may perhaps be called "irritable stomach" in analogy with what others have called "irritable colon". The term is not restricted to the period of the colic, however, and by this definition we have reached the actual crux of our study: Will some of the patients, sooner or later, develop more massive organic changes, if the mental strain persists? Only continued follow-up

studies may possibly, at some later date, answer this question.

It must be borne in mind that modern psychiatry as well as modern cytology (cf. e.g. Leland Clark) are increasingly yielding to the view that eventually any mental process must exhibit biochemical manifestations whether they are measurable or not.

It is well known that easily recognizable emotional tension states may lead to changes in organic function. It is sufficient to refer to the obvious phenomena of blushing, turning pale, sweating, diarrhoea, and a number of allergic reactions, not to mention asthma. To-day evidence is also available of a direct relationship between emotional upsets and disturbances of gastro-intestinal function. Since the psychic component cannot be accurately assessed, inasmuch as it is recognizable only by its effect on somatic functions, continued psychosomatic investigations must rest on the foundation of classic medicine lest it become mere ravings of which we have numerous contemporary examples.

Summary

A group of 135 patients with recurrent abdominal colic of so-called psychogenic nature had X-ray examinations of the stomach and duodenum. Eighty-one of them were examined twice at an interval of three years. The control series consisted of 34 patients of the same category, but without any history of abdominal colic. Symptoms due to maladjustment occurred in 87 %, whereas only 9 % exhibited a purely infectious state. Both the colic group and the controls showed X-ray

changes in the gastric mucosa and in peristalsis. The mucosal changes in the colic group were still present in 75 % at follow-up 3 years later. The increased peristalsis, found in 47 % of the colic group and only in one case of the control group, was still present at follow-up in 68 %. Hypersecretion was found in 41 % and 53 % respectively. Only one patient of the colic group was found to have an ulcer crater, still present at follow-up. In other words, while the follow-up showed that the X-ray

changes of the stomach persisted in almost 75 %, there was subjective improvement—complete or partial disappearance of the abdominal colics—in two-thirds. From this one may conclude that X-ray

changes subside more slowly than subjective complaints, if they do subside entirely. The discussion includes certain considerations in regard to the concept of psychosomatic medicine.

Essai d'étude psychosomatique à propos des douleurs abdominales récurrentes chez les enfants

135 enfants affligés de coliques abdominales récurrentes ont été soumis à des examens radiologiques de l'estomac et du duodenum. 81 de ces enfants ont été soumis à des examens de l'espèce une seconde fois au bout de trois ans. Le groupe de contrôle se composait de 34 sujets témoins appartenant aux mêmes catégories d'âge, mais n'ayant jamais eu de coliques abdominales. Des troubles dus à un défaut d'adaptation à l'entourage ont été relevés respectivement chez 87 et 64 % des sujets de ces deux groupes; par contre, 9 % seulement des sujets affligés de coliques présentaient des états infectieux, alors que dans le groupe de contrôle, 29 % des sujets présentaient de tels états. Dans les deux groupes (et cela respectivement chez 80 et 21 % des sujets) des altérations radiologiques de la muqueuse gastrique et du péristaltisme ont été relevées. La sécrétion gastrique était supérieure à la normale chez 41 % des sujets du premier groupe et chez 53 % des sujets du second groupe. Lors des examens de contrôles pratiqués trois ans plus tard, les altérations de la muqueuse subsistaient chez 75 % des sujets affligés de coliques. Si cet examen de contrôle a révélé que les altérations radiologiques de l'estomac étaient toujours présentes chez 75 % des sujets du premier groupe, une amélioration subjective fut néanmoins constatée dans les deux tiers des cas. Il semble que les altérations radiologiques sont plus lentement influencées que les troubles subjectifs ou même ne subissent aucun changement.

Psychosomatische Stellungnahme zur Frage der rezidivierenden Bauchschmerzen im Kindesalter

Eine Gruppe von 135 Kindern mit rezidivierender Bauchkolik wurde auf Magen und Duodenum röntgenologisch untersucht. Einundachtzig unter ihnen wurden zweimal im Abstand von 3 Jahren untersucht. Die Kontrollserie bestand aus 34 Kranken derselben Kategorie, welche nie an Bauchkolik gelitten hatten. Symptome, die auf schlechte Anpassung zurückführbar waren,

wurden bei 87 % bzw. 64 % der Kranken dieser Gruppen gefunden, während nur 9 % der Kolikgruppe und 29 % der Kontrollgruppe infektiöse Zustände aufwiesen. In der Kolikgruppe als auch unter den Kontrollpersonen (80 % bzw. 21 %) wurden röntgenologisch Veränderungen der Magenschleimhaut und der Peristaltik nachgewiesen. Hypersekretion wurde bei 41 % bzw. 53 % gefunden. Die Schleimhautveränderungen bestanden bei 75 % der Kolikgruppe noch bei der Nachuntersuchung nach 3 Jahren fort. Während die Nachuntersuchung der Kolikgruppe zeigte, dass die röntgenologischen Veränderungen des Magens bei fast 75 % fortbestanden, war jedoch eine subjektive Besserung bei zwei Dritteln der Fälle nachweisbar. Röntgenologische Veränderungen gehen offenbar langsamer zurück als die subjektiven Beschwerden, wenn sie überhaupt gänzlich verschwinden.

Estudio psicosomático del dolor abdominal recurrente en la infancia

Se practicó una exploración radiográfica gastroduodenal a un grupo de 135 niños afectos de cólicos abdominales recurrentes. 81 de ellos fueron examinados dos veces con un intervalo de 3 años. El grupo testigo consistió en 34 pacientes de la misma índole, pero que jamás habían sufrido cólicos abdominales. En el 87 % y 64 % respectivamente de estos grupos se hallaron síntomas debidos a una adaptación deficiente, mientras que solo el 9 % del grupo con cólicos y el 29 % del grupo testigo presentaban estados infecciosos. Tanto en un grupo como en otro (80 % y 21 % respectivamente) se observaron alteraciones radiológicas de la mucosa del estómago y peristaltismo. Se observó signos de hipersecreción en el 41 % y el 53 % respectivamente. Las alteraciones de la mucosa aún persistían en el 75 % de los pacientes del grupo con cólicos, en una revisión efectuada 3 años más tarde. En cambio la revisión del grupo testigo mostró que las alteraciones radiológicas del estómago persistían en casi el 75 %, y en un tercio de los casos existía una mejoría subjetiva. Las alteraciones radiológicas remitieron al parecer mas lentamente que las molestias subjetivas.

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Paediatric Department
Finseninstitutet
Strandboulevard 49
Copenhagen, Denmark

The External Cranial Volume of Normal Children

by J. BALSLEV JØRGENSEN, E. PARIDON and F. QUADE

In pediatric practice, the size of the head, or, more precisely, the volume of the part of the head enclosing the brain, is a measure of considerable interest. Several attempts have been made to compute the volume of the brain by means of formulas incorporating the length, breadth, and height of the head. But as Bröste and his collaborators have shown, this procedure is of little use, seeing that no clear correlation can be found between the calculated values and the directly measured cranial capacity. So far, the early diagnosis of either hydrocephaly or microcephaly has been largely dependent upon simple inspection or measuring the circumference of the head.

In our preliminary experiments, first with dry skulls and later with autopsy material, we described a simple volumetric method, based upon water displacement, of measuring the part of the head which is above the glabella-inion plane. This measure, which we have termed the "external cranial volume" (ECV) proved to be clearly correlated both with the cranial capacity and with the volume of the isolated brain, and at the same time it permitted a more accurate estimate of the said quantities than can be had by measuring the circumference of the head.

We therefore felt justified in extending

our investigations to living children in order to ascertain the normal values of the external cranial volume in its relation to age, height, and weight.

The apparatus is seen in Fig. 1, and Figs. 2 and 3 illustrate the method: an assistant holds the supine child above a container filled with water to the brim. The examiner holds the head of the child with his right thumb on the glabella and his left index finger on the external occipital protuberance, while his right forefinger and left thumb rest on the child's temples in the glabella-inion plane. The head is gently immersed until the surface reaches the examiner's finger-tips, and the displaced water is collected in a measuring-glass. Care must of course be taken not to shake the container during the procedure.

We had not expected the children to put up with this treatment patiently, but actually there was not much trouble. The newborn babies, for one thing, were too weak to upset our arrangements; and the children who were big enough to understand an explanation were mostly willing or even keen on assisting. In between these two groups, however, there were cases where we had to acknowledge defeat: some of the children aged from 1 to 3 kicked up such a row that we had to give up trying to calm them down.

Apart from these children, who had to be left out, we took exception to a few others on our own initiative, viz. children with much more or much longer hair than normal, as we feared that this might influence the accuracy of the results. By repeating the experi-

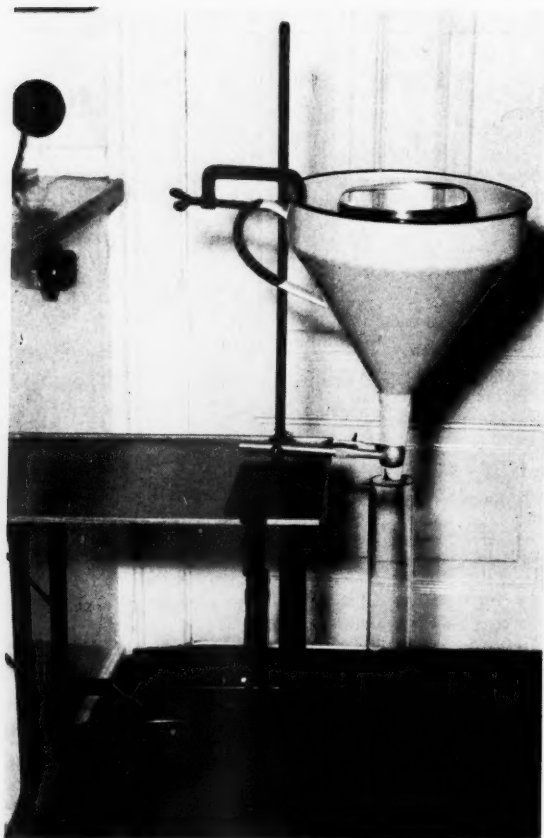


Fig. 1. Apparatus for measuring the external cranial volume.

ment five to ten times on a number of children, we found the standard error on the measure to amount to about 5%. There proved to be no difference in ECV between boys and girls.

The material comprises 215 children, all in good health and coming from maternity hospitals, day-nurseries, and nursery schools; their ages varied from 0 to 7.

Fig. 4, in which ECV is seen in relation to age, shows that the growth of the head is very rapid during the first year of life,

after which time it slows down considerably, so that ECV reaches its final value already at the age of 5 or 6. The distribution of the points allows no simple statistical treatment of the material. The rather astonishing fact that the growth of the head—or, at any rate, the growth of the ECV—seems to be concluded so early, made us measure the capacity of dry skulls from 36 children (Fig. 5), and the volumes of the brains from 14 dead chil-



Figs. 2 and 3. Technique for measuring the external cranial volume.

dren (Fig. 6), but these measurements only served to corroborate our results shown in Fig. 4.

As, however, chronological age is no good biological criterion, we have also examined the relations between the ECV on one side, and height, 'ear height', and body weight on the other. ('Ear height' = total height minus height of head as measured from porion to vertex.) In a normal material, this measure offers no advantages over total height, but when it comes to examining children, especially small children, with heads of a pathological size, total height is misleading as a reference: a short child with hydrocephaly may

have the same total height as a taller, but microcephalic child.

From the next figures it will be seen that the values for ECV versus height (Fig. 7), and for ECV versus 'ear height' (Fig. 8) follow a fairly straight line, and this is even more apparent in the relationship ECV versus body weight (Fig. 9), especially for children below 13 kg. This part of the material, therefore, is best suited for statistical treatment, and so we have analysed the values of the 145 smallest children. A homoscedastical regression analysis of these data gives the following equation:

$$y = 93x + 211,$$

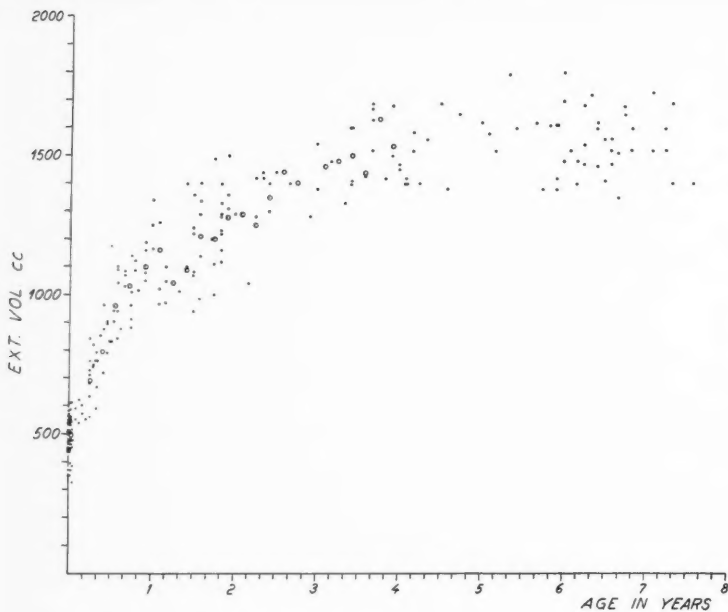


Fig. 4 The relation between age and external cranial volume in 215 children.

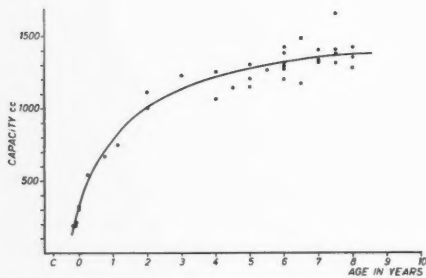


Fig. 5. The relation between age and cranial capacity of skulls in 36 children.

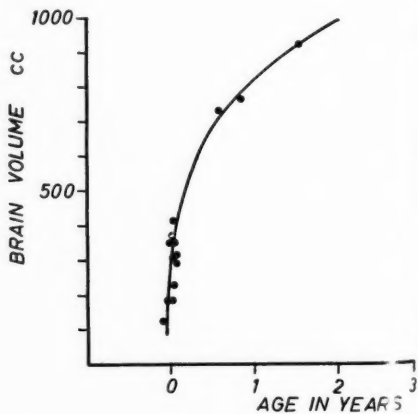


Fig. 6. The relation between age and volume of the isolated brain in 14 children.

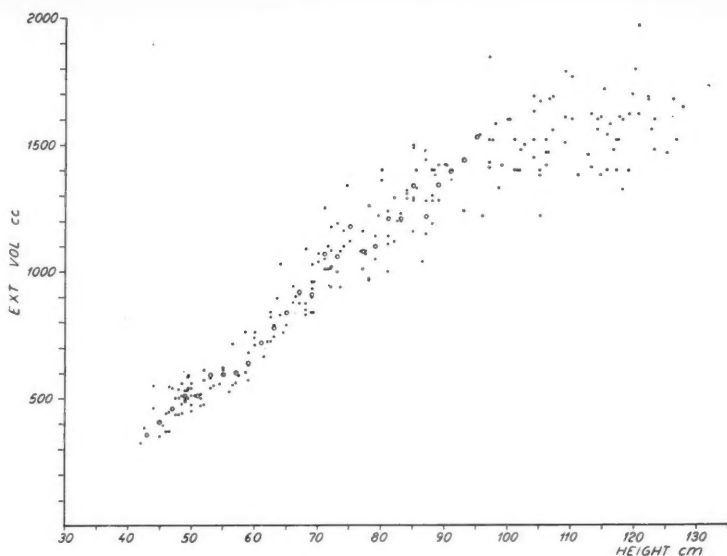


Fig. 7. The relation between total height and external cranial volume.

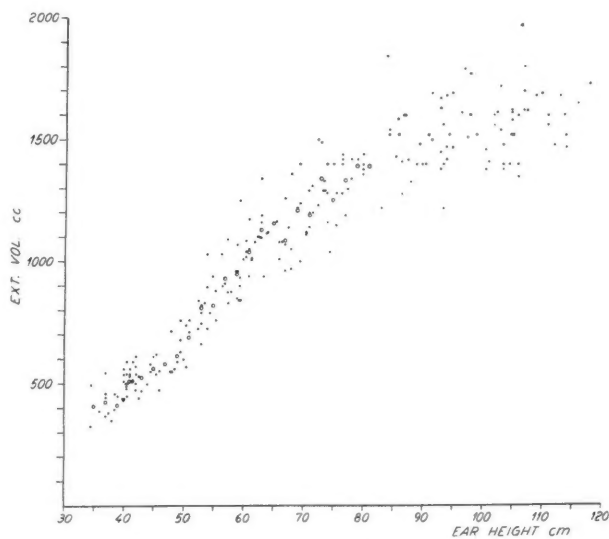


Fig. 8. The relation between "ear height" and external cranial volume.

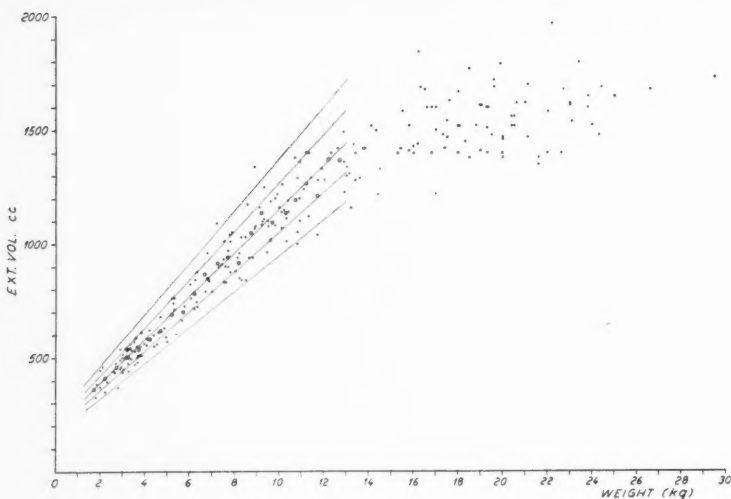


Fig. 9. The relation between body weight and external cranial volume.

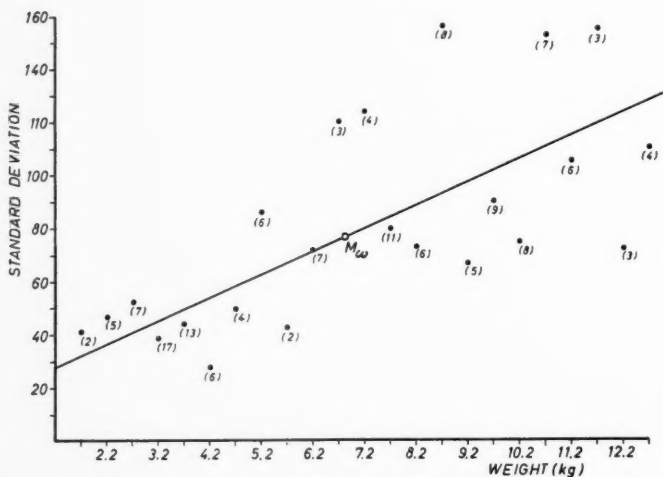


Fig. 10. The relation between body weight and the standard deviation of the external cranial volume.

x being the weight of the child in kg, and y the ECV in cc. The normal deviation around the mean values represented by the above equation cannot be calculated by simple means, seeing that the points

show an increasing spread as we move from left to right in Fig. 9. The standard deviation has to be computed for each weight section separately, and in Fig. 10 its values are given for each half-kg inter-

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val. If we make a regression analysis here, we get this equation:

$$s = 8.7x + 18,$$

where s is the standard deviation for ECV of children with the weight x kg. By drawing—in Fig. 9—four lines representing once and twice the standard deviation above and below the line for mean values, we delineate two areas, within which lie, respectively,* 68 % and 95 % of normal children's ECV-values. It now becomes possible to decide whether or not a child

of a certain weight has a head of normal size, and it is our hope that the method described in this paper can be put to practical use.

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Summary

The "external cranial volume" (ECV: the volume of the part of the head which is above the glabella-inion plane) can be measured by a simple method based upon water displacement. The ECV permits a more accurate estimate of the brain volume and of the cranial capacity than can be had by measuring the circumference of the head. Based upon a material of 215 healthy children, the normal values are given for ECV in its relation to age, height, and weight.

Mesurage du volume crânien externe chez l'enfant normal

Le volume crânien externe (V.C.E), c'est-à-dire la partie de la tête se trouvant au dessus d'une ligne passant par la glabelle et la protubérance occipitale externe (inion), peut être mesuré par une méthode simple basée sur le déplacement d'eau. La connaissance de cette mesure permet d'obtenir une meilleure estimation du volume du cerveau et de la capacité crânienne que la mesure de la circonférence de la tête. La recherche se fonde sur l'examen de 215 enfants bien portants; les valeurs normales sont établies en relation avec l'âge, la taille et le poids.

Das äussere Schädelvolumen normaler Kinder

Das äussere Schädelvolumen, d. h. der Inhalt des Teils des Schädels, welcher oberhalb der Glabella-Occipitalprotuberanz-Ebene liegt, kann mit Hilfe einer einfachen auf Wasserverdrän-

gung beruhenden Methode gemessen werden. Die Kenntnis des äusseren Schädelvolumens ermöglicht eine genauere Schätzung des Hirnhalts und des Schädelraumes, als dies mit Hilfe der Messung des Kopfumfanges möglich ist. Auf Grund eines Untersuchungsmaterials von 215 gesunden Kindern werden die Werte für das äussere Schädelvolumen und seine Beziehung zu Alter, Körpergrösse und Gewicht angegeben.

El volumen craneano externo en el niño normal

El volumen craneano externo (E.C.V.), o sea la parte del cráneo que se encuentra por encima del plano glabella-inión, puede ser medido por un método simple basado en el desplazamiento del agua. Es sabido que el E.C.V. permite una apreciación más exacta del volumen cerebral y de la capacidad craneana que la obtenible por la medida de la circunferencia cefálica. Son dados los valores normales del E.C.V. y su relación con la edad, peso, y estatura, tomados de un material de 215 niños sanos.

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Ostersøgade 26
Kopenhagen K
Denmark

A Dermatoglyphic Study of the Palms of Mongoloids, Imbeciles and Normal Subjects

by ILKKA HÄKKINEN and EINO LUNDELL

The purpose of this study is to determine the dermatoglyphic differences in mongolian idiots and normal children, to assess the significance of such differences and to find out whether special dermatoglyphic features are evident in the parents of mongoloids that might be of diagnostic value.

Material and Methods

One of the groups studied comprised 36 previously diagnosed mongolian idiots who had all the usual mongolian characteristics (1, 2, 3, 5). Another group consisted of all other members, 47 in number, of the families of 13 mongolian idiots. The third group comprised 24 imbeciles. The fourth group, the control group, consisted of 42 healthy subjects. All the subjects lived in Turku or Porvoo.

Palm prints of the right hand were taken from all the subjects and the dermatoglyphic features in these were classified by the method of Turpin *et al* (6). The dermatoglyphic features examined were the following:

- 1 The course of the papillary lines of the distal part of the palm. The papillary indexes were evaluated from the observations (see figure 1).

- 2 The location and configuration of the hypothenary coils curls. These may open either radially or ulnarly or may be altogether absent.

- 3 The hypothenary papillary crossings

(axial triradix), which may be located proximally, centrally or distally.

4. Ape line dermatoglyphs in normal and mongolian individuals are shown in Figs. 1 and 2.

Results

The mean papillary index for the group of mongolian idiots was found to be 31.4. The highest value was 36 and the lowest 23.

Hypothenary curls opening ulnarly were seen in 27 of the mongolian idiots, but absent from 9. No curl that opened radially was found in the series. The hypothenary papillary crossings were situated proximally in two, centrally in none, and distally in 34 of the idiots. The ape line was seen in 28 and absent in 8 palms.

Dermatoglyphs were found in the palms of other members of the families of the mongoloids as follows: The mean papillary index was 29.65, the highest index 34 and the lowest 19. The hypothenary curl was absent from the palms of 39 individuals, opened radially in 3 and ulnarly in 5 cases. Hypothenary papillary crossings were found located proximally in 36, centrally in 8, and distally in 43 individuals. Four of the relatives had ape lines.

The mean papillary index in the group of imbeciles was 29.3, the highest value



Fig. 1. Palm print of a normal hand. The edge of the palm is divided into sections which are numbered as shown. Areas of the palm adjoining the fingers, the thumb excepted, are designated by the letters *a-d*. By following the palm lines from the roots of the fingers one comes to one of the numbered sections. In this way four numbers are obtained whose sum gives the papillary index. For the hand shown the papillary index is $a5 + b5 + c5 + d7 = 20$. Hypothenary papillary crossing (axial triradix) is proximally located. The ape line is absent.

being 52 and the lowest 22. The hypothenary curl was absent from 21, opened ulnarly in 1, radially in 1, and a curl opening both ulnarly and radially was found in one imbecile. The hypothenary papillary crossings were located proximally in 16, centrally in 4 and distally in 4. Ape lines were seen in two individuals, but were absent from 22. In the central group, the papillary index varied from 21 to 35, with a mean index of 28.9. The hypothenary curl was absent from 36 palms, opened radially in 5 palms, and opened both ulnarly and radially in the

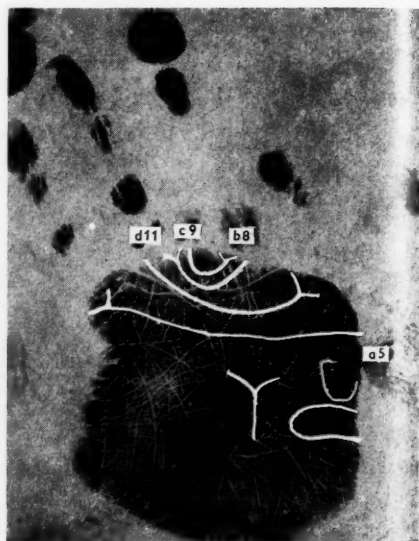


Fig. 2. Palm print of a mongolian infant. The papillary index $a5 + b8 + c9 + d11 = 33$. A hypothenary curve is seen that opens ulnarly. The axial triradix is situated more distally than in Fig. 1. An ape line can be distinguished.

palm of one individual. The hypothenary crossings were proximally located in 36, centrally in 5, and distally in 1 individual. No ape lines were seen in the group.

Discussion

Ape lines were absent from the palms of 8 mongoloids. All of them had a hypothenary curl that opened ulnarly and a hypothenary papillary crossing that was distally located. Their mean papillary index was 31.00. The hypothenary curl was not found in eight mongoloids. Two of the latter had a proximally located hy-

TABLE 1.

	Ape line	Ulnar curl	Distal axial triradix	Mean index
Mongoloids	77.78 %	75 %	94.4 %	31.36
Siblings and parents of mongoloids	8.5 %	10.6 %	6.4 %	29.7
Imbeciles	8.3 %	4.2 %	16.7 %	29.2
Controls	0.0 %	0.0 %	2.3 %	28.9

pothenary papillary crossing, one of these had a papillary index of 31, the other eight an index 31 or higher. Ape lines were found in the palms of all the mongoloids. Of the dactyloglyphic characters found to be prevalent in the mongoloids, a single character was seen in 21 members of their families, two characters in two, and three characters in only one member.

Imbeciles had one character that prevailed in the mongoloids in 4 cases, two characters in 3 cases, and three characters in one case.

One of the characters seen in the majority of mongoloids were noted in 6 individuals of the control group, but none of the latter had two or three characters.

The incidences of dermatoglyphic characters typical of mongoloids and mean papillary indices in the groups of the present study are given in Table 1. The relative incidences of these characters in the mongoloids are higher than those reported by Turpin *et al.* The values for the group of imbeciles are higher than those for the control group. The values for these two groups and also those for the other members of the families of the mongoloids are definitely lower than those for the group of mongoloids, which is in accord with the findings of Turpin *et al.* (6). The labyrinthic pattern of palm texture described by Heller (4) does not appear to develop be-

fore the mongoloids are several years old; this is possibly connected with the flabbiness of the skin (with cutis laxa).

The present study of dermatoglyphic characters in previously diagnosed mongoloids shows that the occurrence of several characters and a papillary index higher than 31 strongly points to mongolism. On the other hand, the existence of a single dermatoglyphic character of this type cannot be ascribed any diagnostic significance.

The results for the other members of the families of the mongoloids indicate that mongolian characters are more often evident in their palms than in those of other persons. The same conclusion was drawn by Heller (4), who considered genetic factors responsible for the development of these characters. We encountered one non-mongolian member of a mongoloid's family who had three unusual dermatoglyphic characters. This suggests that mongolism is an inherited defect.

The mean incidence of dermatoglyphic characters in the palms of imbeciles was closer to the incidence in the group of mongoloids than the incidence in the control group. Heller (4) did not observe any differences in this respect between non-mongolian idiots and controls.

As far as the question is concerned whether the palm texture typical of mongoloids is solely a sign of defective development or a special characteristic of this group, our observations that deviations from normal occurred in the imbecile group would suggest that such a texture is a manifestation of general defectiveness.

Summary

The dermatoglyphic characters of the palms of mongoloids, imbeciles and normal

subjects have been compared to determine whether the occurrence of such characters

may be of value in the early diagnosis of mongolism.

Étude dermatoglyphique des paumes de sujets mongoloïdes, imbéciles et normaux

L'auteur s'est livré à une étude comparative des caractères dermatoglyphiques de sujets mongoloïdes, imbéciles et normaux afin de déterminer si l'apparition de caractères de l'espèce pourrait être de quelque utilité pour le diagnostic précoce du mongolisme.

und normalen Personen wurden verglichen, um zu entscheiden, ob das Vorkommen solcher Kennzeichen für die Frühdiagnose des Mongolismus verwertet werden könnte.

Estudio dermatoglífico de las palmas de las manos de mongoloïdes, imbéciles e individuos normales

Se han comparado los caracteres dermatoglíficos de las palmas de las manos de mongoloïdes, imbéciles e individuos normales para determinar si estos caracteres podían tener utilidad en el diagnóstico precoz del mongolismo.

Dermatoglyphstudie der Handflächen von mongoloiden, schwachsinnigen und normalen Personen

Die dermatoglyphischen Charakterzüge der Handflächen von mongoloiden, schwachsinnigen

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Pediatric Clinic
University of Turku
Turku, Finland

The Effect of Food and Growth on the Metabolism of Phosphorus in the Newly Born

by E. M. WIDDOWSON and R. A. McCANCE

The concentrations of calcium and phosphorus in the serum of the newborn baby have been studied by various investigators both for the intrinsic interest of the problems involved and in connection with tetany of the newborn (Bakwin, 1937; Todd, Chuinard & Wood, 1939; Gardner, MacLachlan, Pick, Terry & Butler, 1950). There is a general tendency to consider that the serum calcium falls in the first two days after birth, and that this is often accompanied and perhaps accentuated by a rise in the serum phosphorus, which is itself later increased by the high intake of phosphorus if cow's milk is administered. Much less consideration has been given to the excretion of phosphorus, but it has been known to be very small in the first 48 hours of life since Heubner (1910) investigated the matter in his own healthy baby. McCance & Widdowson (1954) showed that the urine passed at birth and in the first 24 hours of life contained practically no phosphorus unless labour had been prolonged and difficult, but that it began to appear in appreciable amounts towards the end of the second 24 hours. Few investigations seem to have been made on animals other than man.

The experiments now being reported shed rather a new light on the subject and emphasise the importance of food and growth as homeostatic agents in the newborn animal (McCance & Widdowson, 1956, 1957, 1958).

Material and Methods

The experiments were conducted on normal male full term infants and on newborn pigs. Urine was collected from the babies at birth and for the first 48 hours of their lives in two 24 hour periods, and from some of them again for 24 hours on the seventh day of life after feeding had become established. Breast fed babies and babies fed on cow's milk preparations were included. Blood was taken without anticoagulant from the cord and from the mother at delivery and by heel prick when the babies were 48 hours and 7 days old. The serum was separated at once. In all, 55 babies have been studied, but complete data were obtained on only ten of them. The babies were put to the breast every 4 hours from the time they were 6 hours old, and those to be reared on cow's milk were given half strength Ostermilk No. 1 at these times. The amount of milk involved, however, was very small. On the seventh day the babies took about 450 ml of breast milk or of reconstituted Ostermilk No. 1.

The newborn pigs were placed in metabolism cages soon after they were born and before they had been fed by the mother, and given similar amounts of water or sow's milk by stomach tube at two-hourly intervals by a technique which has previously been described (McCance & Widdowson, 1956).

The phosphorus in the serum and urine was determined by the method of Fiske & Subbarow (1925). The intake of phosphorus was estimated by test weighing the babies and analysing samples of breast milk, or, in the case of the piglets and of the infants on the cow's milk preparation, from an analysis of the milk, which was administered in known amounts. The technique used was to dry weighed samples of milk, ash them at 450°C, and apply the method of King (1932) to the HCl extract of the ash after heating with H₂SO₄ (one drop per ml) for one hour in a boiling water bath to convert any pyrophosphate to orthophosphate.

Results

Table 1 shows a comparison between the concentration of inorganic phosphorus

TABLE 1. *The concentrations of phosphorus in the sera of the mothers and breast-fed babies and urinary excretions of phosphorus during the first two days of life.*

	Average	No. of com- pari- sons
Phosphorus in mother's serum, mg/100 ml	3.90	22
Phosphorus in serum from cord blood, mg/100 ml	5.90	
Phosphorus in serum from cord blood, mg/100 ml	6.12	15
Phosphorus in baby's serum 48 hours after birth, mg/100 ml	7.91	
Urinary excretion of phosphorus on first day, mg/kg body weight/24 hours	0.242	24
Urinary excretion of phosphorus on second day, mg/kg body weight/24 hours	4.156	

in the serum of the mother at delivery and in the cord blood, and between the serum at birth and at 48 hours. The number of comparisons is shown in each case. The concentration of phosphorus in cord blood was significantly higher than that in maternal blood ($t = 7.9$; $p < 0.01$), and the rise during the first forty-eight hours of life was also statistically significant ($t = 4.44$; $p < 0.01$). Table 1 also shows the urinary excretion of phosphorus by twenty-four babies during the first two days after birth. The urinary excretion was significantly higher on the second day than the first ($t = 3.1$; $p < 0.01$). The intake of phosphorus up to this point had been in all babies negligible.

By the seventh day the average intake of phosphorus by 14 breast-fed infants had risen to 20 mg/kg/day, but in spite of this, the excretion of phosphorus in the urine had fallen to 0.35 mg/kg/day. The serum phosphorus at this time averaged 6.8 mg/100 ml. Six babies fed on a cow's milk formula had phosphorus intakes of about 100 mg/kg/day on the seventh day, and the urines contained 40 mg/kg/day which was much more than they did in babies fed on breast milk or in any of the babies during their first 48 hours. The serum concentrations are known to be higher on such a régime than they are on breast milk and in this investigation averaged 9.0 mg/100 ml (Gardner *et al.*, 1950; Smith, 1951).

Table 2 shows the intakes and excretions of phosphorus by newborn pigs which were given milk and gaining weight, and by litter mates which were given water and losing weight. In spite of the large amounts of phosphorus ingested with the milk, the animals given this food excreted much less

TABLE 2. *The intakes and excretions of phosphorus in starving and well-fed piglets.*

Expt.	Duration of expt. h	Intakes and excretions of phosphorus, mg/kg/24 hours			
		Piglet on water alone		Piglet on sow's milk	
		P in	P out	P in	P out
1	40	0	15.2	352	0.6
2	40	0	7.3	420	1.8
3	40	0	11.0	370	1.7
4	27	0	6.9	435	2.6
Av.		0	10.1	394	1.7

phosphorus in the urine than those given nothing but water.

Discussion

These experiments emphasise the capacity of the newborn baby to incorporate the phosphorus in breast milk into its own tissues as one of the consequences of growth. The results suggest that the rise in the serum concentrations and urinary excretions during the first 48 hours of life are manifestations of starvation and tissue breakdown, and the results on piglets indicate that this is a general phenomenon common to other species. These findings differ from those which have usually been found in healthy adults (Benedict, 1915; Lusk, 1928). In them starvation, certainly prolonged starvation, has been found to reduce the excretion of phosphorus, for there has been no growth to a point for any of the phosphorus ingested before the fast, and normal intakes have usually exceeded the amounts excreted during starvation. Benedict, however, found a further and very pronounced fall in the excretion of phosphorus on the first,

second and third days after reintroducing food. Presumably tissue restoration in his adult was providing the stimulus for phosphorus retention which growth provides in the infants. Gamble, Ross & Tisdall (1923) made observations similar to those of Benedict after a period of starvation in older children aged 8-12 years. The results for the present babies on cow's milk show that, when the intake of phosphorus was sufficiently high, the capacity of the baby to incorporate phosphorus into its growing tissues was more than saturated, and the excess was excreted in the urine. The effects of food and starvation appear to be just the same in the newborn pig as they are in the human baby, and the amount of phosphorus in sow's milk to be very nicely adjusted to the needs of the growing animal. It is to be noted that the average intake of phosphorus by the piglets was 20 times as high as the intake by the breast fed babies; this is unquestionably related to their more rapid rate of growth. Since some of the babies getting breast milk excreted only traces of phosphorus on the seventh day, it is open to question whether their capacity to incorporate phosphorus into their growing tissues at that time was completely saturated.

There is no doubt that the renal clearances of phosphorus at this time of life depend upon the magnitude of the intakes and the activity of the parathyroid glands (Dean & McCance, 1948; Gardner *et al.*, 1950; McCrory, Forman, McNamara & Barnett, 1952), but a consideration of this appears to lie outside the scope of the present investigation. It does not affect the interpretation of the results.

Summary

1. The intakes and excretions of phosphorus were studied in newborn babies and piglets when they were getting little or no food and when they were fully fed.

2. On the food provided by nature the serum concentrations and the urinary excretions were lower than they were during periods of absolute or relative starvation.

3. On cow's milk mixtures the infants 7

days old excreted more phosphorus than they did on breast milk or during the relative starvation of the first 48 hours of life.

4. Some of these results have been explained as the consequences of starvation and the rest as being due to the capacity of the newborn animal if growing to incorporate the phosphorus of its mother's milk into its tissues.

Influence de l'alimentation et de la croissance sur le métabolisme du phosphore chez les nouveau-nés

L'auteur a déterminé les quantités de phosphore ingérées et excrétées par des enfants-nouveaux-nés et des cochons de lait à des époques où ils ne recevaient que peu ou pas de nourriture et à des moments où ils étaient normalement alimentés. Les concentrations sanguines et les taux d'excrétion urinaire trouvés après une alimentation naturelle furent moins élevés que les taux enregistrés chez les sujets soumis à une privation relative ou totale de nourriture. Les bébés de 7 jours alimentés au lait de vache éliminaient des quantités de phosphore plus importantes que celles excrétées lorsqu'ils étaient nourris au lait maternel ou au cours des 48 premières heures de leur vie où ils étaient relativement privés de nourriture. Ces résultats s'expliquent par les phénomènes que l'on observe normalement après une privation de nourriture ainsi que par l'aptitude de l'animal nouveau-né en période de croissance d'incorporer du phosphore dans ses tissus si les quantités ingérées ne dépassent pas celles présentes dans ses aliments naturels.

Die Wirkung von Nahrung und Wachstum auf den Phosphorstoffwechsel von Neugeborenen

Die Phosphor-aufnahme und -ausscheidung wurde bei neugeborenen Kindern und Schweinen, wenn sie wenig oder gar keine Nahrung erhielten und, wenn sie voll ernährt wurden, studiert. Bei

der von der Natur gebotenen Nahrung waren die Konzentrationen im Serum und Ausscheidungen im Harn geringer als während der Perioden von absolutem oder relativem Hungern. Bei Kuhmilchmischungen schieden die 7 Tage alten Kinder mehr Phosphor aus als bei der Brustmilchernährung oder während des verhältnismässigen Hungerns in den ersten 48 Lebensstunden. Diese Ergebnisse wurden als normale Folgen des Hungerns und der Fähigkeit des wachsenden neugeborenen Tieres, Phosphor in seine Gewebe einzuverleiben, wenn die aufgenommenen Mengen die in der natürlichen Nahrung vorhandenen nicht überschreiten, aufgefasst.

Efecto de la alimentación y del crecimiento sobre el metabolismo del fósforo en los recién nacidos

Se estudiaron la ingesta y la excreción de fósforo en niños y cerditos recién nacidos cuando se les administraba escaso o ningún alimento, y cuando su alimentación era completa. Con la alimentación natural, la concentración en suero y la excreción urinaria eran menores que durante los periodos de inanición absoluta o relativa. Con las mezclas de leche de vaca, los niños de siete días excretaban más fósforo que con la leche materna o durante la inanición relativa de las primeras 48 horas de vida. Estos resultados se explican por los resultados normales de la inanición y por la capacidad del recién nacido para incorporar fósforo a sus tejidos si la cantidad ingerida no excede a la contenida en su alimentación natural.

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Department of Experimental Medicine
University of Cambridge
Cambridge, England

CASE REPORT

Diabetes Mellitus Following Smallpox Vaccination

by C. CHOREMIS, E. BAROUTSOU and K. KIOSSOGLOU

Pediatric Clinic of Athens University

Case Report

P. A., a 16 months old female, well developed and nourished, was admitted on January 4, 1958 because of sudden onset of polyphagia, polydipsia and polyuria since Dec. 27, 1957. Past and family history of no importance. She had been vaccinated with diphtheria-tetanus toxoid at the age of 6 months. Twelve days prior to the onset of symptoms (Dec. 15, 1957), she was successfully vaccinated against smallpox.

Physical examination on admission was negative except for the presence of a small rounded pustule at the site of vaccination in the skin of the left deltoid area.

Laboratory findings: Tuberculin skin test with O.T. 10 U neg. White blood cells 8000/mm³ with differential count polymorphonuclears 46%, lymphocytes 54%. Hemoglobin 11 g%.

Twenty-four hours' urine, 500 ml approximately. Urinalysis: reaction acid, albumin (-), glucose 4 g%, acetone (+). Fasting blood sugar 120 mg%.

The patient was given regular insulin 5U three times daily and a diet of 1100 calories daily (carbohydrates 120 g, protein 60 g and fat 40 g).

On Jan. 5, 1958, the amount of 24 hours' urine was reduced to 400 ml, and the urine sugar to 1.2 g%; the acetone disappeared. Next day there was no glucosuria and the fasting blood sugar was 65 mg%. The administration of insulin was discontinued on

Jan. 8, but two days later the patient again developed glycosuria, although some urine samples were free from sugar and the amount of urines per 24 hours ranged between 300 and 400 ml. Fasting blood sugar on Jan. 10 was 106 mg%. On Jan. 12, 1958, a glucose tolerance test using glucose 2.5 g per kg of body weight orally resulted in the following glycemic curve. Fasting level 106 mg%; at 30 min. 180; 60 min. 260; 120 min. 330; and at 180 min. 300 mg%.

Both parents of the patient exhibited a normal glycemic curve following a similar glucose loading.

The child was discharged on Jan. 14, with a normal fasting blood sugar, no polyuria or ketonuria but with intermittent glycosuria. She was given the same diet but no insulin. The parents were recommended to attend frequently the out patients department and test the urine for sugar daily.

The patient was readmitted on Jan. 21, 1958, because of glycosuria and ketonuria.

Initial laboratory findings showed fasting blood sugar 140 mg%, urine glucose 4 g% and acetone (+). The administration of regular insulin was resumed in the dose of 5U three times daily, and 24 hours later the ketonuria disappeared while glycosuria was detected only occasionally. On Jan. 27, her urine was entirely free from glucose. Repeated glucose tolerance tests were as abnormal as the first one. During the above period of time the fasting blood sugar had always been above 135 mg% in spite of the

administration of insulin 5 U three times daily and the diet above described. On Feb. 5 the treatment was modified by administering 5 U of crystalline plus 5 U of protamin-zinc insulin in the morning and 5 U of crystalline insulin the evening.

The patient was discharged on March 9, 1958, and since then is being closely followed up in the outpatient department. She is free of any clinical symptoms, her growth and development is normal, and now, at the age of 27 months, she weighs 16 kg. Her daily insulin requirements under free diet range between 18 and 24 U of protamin-zinc insulin administered each morning. On no occasion has she had any ketonuria although she still has intermittent glycosuria. Her fasting blood sugar range between 98 mg % and 159 mg %. Owing to faulty administration of insulin she has developed on six occasions slight hypoglycemia while once she had had a fasting blood sugar of 387 mg %.

Discussion

It has been estimated that 5-8 per cent of all cases of diabetes mellitus appear in the pediatric age group. It occurs even during the first year of life. Diabetes mellitus in infants and young children, particularly at the early stages, may manifest itself with minimal and inconstant hyperglycemia as well as with intermittent glycosuria (3). The diagnosis can be safely confirmed only by an abnormal glycemic curve following a glucose tolerance test. When one or both parents are diabetic, this metabolic defect may be attributed to hereditary factors. In the apparent absence of such factors it is almost never possible to find a satisfactory explanation for the appearance of the disease in early life.

It is a well-established fact that infection and injuries may precipitate the man-

ifestation of a latent diabetes mellitus or aggravate an already apparent disease. However, nobody has ever postulated that infections or other injurious factors can be exclusively responsible for the development of diabetes mellitus.

Our patient developed the typical clinical symptomatology of diabetes mellitus twelve days following smallpox vaccination. She had intermittent glycosuria and ketonuria but no appreciable hyperglycemia. A short-term treatment with small amounts of insulin resulted in disappearance of ketonuria as well as significant decrease of glycosuria. The diagnosis was firmly established only after obtaining a diabetic glycemic curve following a glucose tolerance test. When the patient was readmitted thirty-seven days following smallpox vaccination the disease was fully established with a definitely high fasting blood sugar.

The close time-relationship between smallpox vaccination and the development of diabetes mellitus cannot be disregarded with certainty. Of course, it is impossible to decide whether the vaccination was responsible for the development of the disease or it simply precipitated a latent diabetes. Furthermore it is impossible even to speculate the trigger mechanism through which the vaccination might have caused such a serious metabolic disturbance.

It may be mentioned that several years ago we saw another 18-month-old child developing symptoms of diabetes shortly after smallpox vaccination; however, the symptoms were transient and since then the child has remained healthy and has shown no evidence of disturbed carbohydrate metabolism.

Summary

A 16-month-old child developed diabetes mellitus 12 days after smallpox vaccina-

tion. The possibility that the vaccination might have caused this metabolic disturbance is discussed.

Diabète sucré consécutif à une vaccination antivariolique

Une petite fille de 16 mois a été atteinte de diabète sucré 12 jours après une vaccination antivariolique. L'éventualité que la vaccination a joué un rôle dans la genèse de ce trouble du métabolisme est discutée.

Diabetes mellitus im Anschluss an Pockenschutzimpfung

Ein 16 Monate altes weibliches Kind entwickelte Diabetes mellitus 12 Tage nach er-

folgter Pockenschutzimpfung. Die Möglichkeit, dass die Impfung die Ursache dieser Stoffwechselstörung gewesen sein mochte, wird erörtert.

Diabetes mellitus consecutiva a la vacunación antivariólica

Una niña de 16 meses desarrolló una diabetes mellitus a los 12 días de la vacunación antivariólica. Se discute la posibilidad de que la vacunación pueda haber provocado el trastorno metabólico.

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"St. Sophie's" Children's Hospital
Athens, Greece

CASE REPORT

Generalized Cytomegalic Inclusion Disease

by S.-I. BJÖRKLUND and O. WIEBERT

From the Flensburg Children's Hospital (Head: Per Selander, M.D.) and the University Department of Pathology (Head: Folke Linell, M.D.), General Hospital, Malmö, Sweden.

The first case of generalized cytomegalic inclusion disease was observed in 1881 by Ribbert, who did not report it until 1904, and then under the name of "Krankheit mit protozoenartigen Zellen". In view of the close resemblance between the inclusion bodies pathognomonic of the disease and the inclusion bodies seen in known virus diseases as well as between the latent forms of the disease limited to the salivary glands and virus diseases of the salivary glands in certain rodents, it was gradually assumed that generalized cytomegalic inclusion disease was due to some virus. It has as yet not been possible to transfer the disease to laboratory animals.

In recent years serious attempts have been made to isolate the agent responsible for the disease. Thus Smith succeeded in isolating a filtrable factor from salivary glandular tissue and from renal tissue from children with generalized cytomegalic inclusion disease. On tissue culture this factor gave growth of intranuclear inclusions. From the liver and urine from 2 cases of cytomegalic inclusion disease Weller *et al.* isolated an agent which *in vitro* produced cytopathic changes character-

ized by intranuclear inclusions. They also demonstrated the presence of antibodies not only in children with generalized cytomegalic inclusion disease but also, and not so rarely, in normal adults.

It does not appear unreasonable to assume some causal relationship between the human salivary gland virus and generalized cytomegalic inclusion disease. The typical large cells with intranuclear inclusions are said to be demonstrable in the salivary glands of 10–30 per cent of all children coming to routine autopsy (Mercer *et al.*).

The clinical picture is dominated by purpura, icterus and hepatosplenomegaly. The disease is usually fatal, though a few cases are on record in which the patients survived the acute stage, though usually with permanent cerebral sequelae. In almost all known cases the disease was not diagnosed until *post mortem*. Wyatt *et al.* suggested that it might be possible to diagnose the disease *ante mortem* by cytologic examination of the urine, and in 1952 Fetterman and Mercer *et al.* succeeded in doing so (for ref. see Medearis).

The disease is known in Europe, U.S.A. and Asia. It has been described in Finland



Fig. 1. Case of generalized cytomegalic inclusion disease with distinct petechiae. One day old.

(Ahvenainen), but has apparently not been described in the other countries of Scandinavia.

This paper is concerned with a fatal case in which examination failed to reveal any inclusion bodies in the urine *ante mortem* despite an abundance of such inclusions in the kidney *post mortem*.

Report of case

Baby girl, born on July 10, 1957, two weeks before term. Birthweight 1900 g. Both parents were healthy and pregnancy had been normal.

Just before the birth of the patient an older brother had been admitted to hospital with a provisional roentgen diagnosis of inflamed cystic lung lesions. The alterations responded to antibiotics and the patient was

discharged as cured. He has not been examined in hospital since.

The child was immediately after birth transferred to the Department of Paediatrics because of its immaturity. The tone of her cry was healthy. The skin was grey-icteric and showed abundant petechiae (Fig. 1). Her physical condition appeared to be good but soon deteriorated. Abdominal distension and jaundice increased during the following days. After 1 day the liver was slightly enlarged but the spleen in the tympanitic abdomen could not be palpated with certainty. No other abnormalities were observed during the next few days. The child was fed with human milk by drip. At one week of age severe diarrhoea occurred and proved refractory to dietary measures and antibiotics, and the general condition of the infant became worse. Jaundice persisted, new petechiae appeared, and the child died at 26 days of age. The results of blood studies are given in the table. Examination of the urine on 3 occasions failed to reveal any inclusion bodies.

TABLE 1.

Age in days	Hb, %	Leucocytes	Polymorphonuclear leucocytes, %	Thrombocytes	Reticulocytes, %	Prothrombin index	Bilirubin (mg/100 ml)
1	150	14,700	28	145,000	56	48	17.5
2	150	17,500	52	168,000	58		
3	142	9,500	45	147,000	29	89	13.8
19	86	21,700	59	96,000	0		6.4

Autopsy.—A delicate child (wt. 1640 g) with grey-icteric skin. The body was covered with punctate to confetti-sized petechiae of varying age. The abdomen was severely distended.

The serous membranes showed numerous punctate haemorrhages. The heart was of normal size and shape. The pericardium contained a tiny amount of clear yellow fluid. The surfaces of the lungs showed varying

Fig. 2

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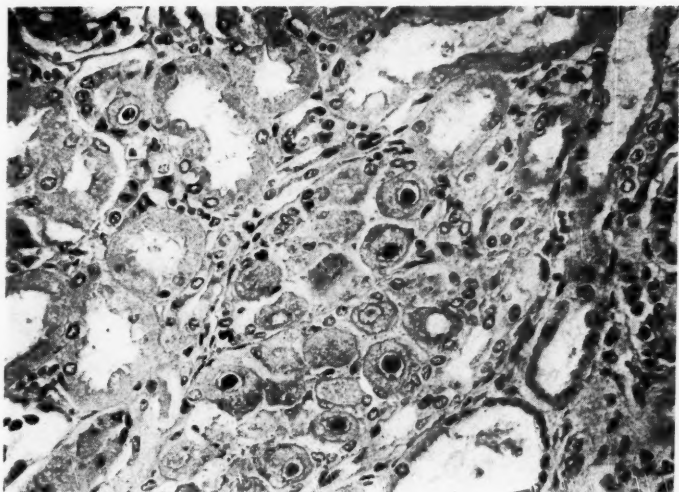


Fig. 2. Kidney. In the middle is a duct with large, partly desquamated epithelial cells containing big intranuclear inclusion bodies surrounded by pale haloes. Haematoxylin-eosin.

sized and sometimes confluent red-blue haemorrhagic patches. The salivary glands were of normal gross appearance.

The abdominal cavity contained 20 ml of clear yellow fluid. The liver was markedly enlarged (wt. 180 g) and dark green. The spleen was also enlarged (wt. 30 g). The pancreas was of normal appearance.

The kidneys were brown-green and of normal size (total wt. 18 g). The mucosal lining of the renal pelvis was of icteric hue. The total weight of the adrenals was 2 g. The meninges were normal. No changes were seen in the cerebral parenchyma. No signs of kernicterus.

Histologic examination.—Some parts of the lungs were studded with haemorrhages but no signs of interstitial pneumonia were seen. Here and there the alveolar epithelium contained an inclusion body.

The architecture of the cut surface of the liver was normal. There was no fibrosis. A few typical inclusion bodies were seen in the epithelium of the bile ducts but not in the liver cells. No bile thrombi were noted. The liver showed extramedullary blood forming foci. The kidneys contained numerous in-

clusions, mainly in the tubular epithelium of the convoluted tubules, occasionally also in Henle's loop. But no inclusions were seen in the glomeruli. The affected cells were markedly enlarged (diam. 20–25 μ). The ratio between the size of the nucleus and that of the cytoplasm was practically normal. The usually dislocated nucleus contained an acidophilic inclusion body, which on higher magnification was found to be built up of numerous small round bodies. This inclusion was surrounded by a pale halo within the nuclear membrane, the inner surface of which was lined with partly condensed chromatin (Fig. 2). Towards the basal membrane the cytoplasm was often foamy, but it did not take on fat stains. The cytoplasmic inclusions were crowded together in crescent shaped formations in the luminal poles of the cells. The inclusion bodies consisted of basophilic round bodies without any surrounding pale halo (Fig. 3). Here and there the tubules contained desquamated, enlarged epithelial cells, some of which contained intranuclear inclusions, while in others the nucleus showed only a space evidently once occupied by inclusions that had in the meantime been

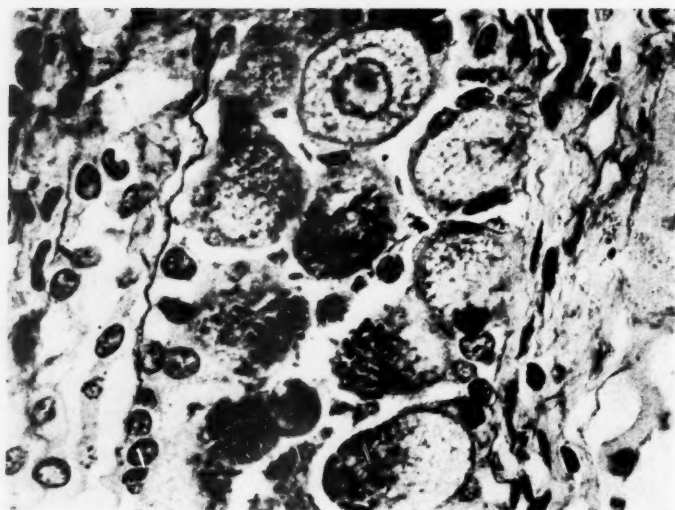


Fig. 3. Kidney. Group of epithelial cells with numerous cytoplasmic inclusions. Staining according to McManus.

desquamated. No definite signs of interstitial nephritis were observed. Extramedullary blood forming foci were also seen in the kidney.

A fairly large number of cells containing inclusions were found in the exocrine pancreatic parenchyma, but not in the islands. The pancreas showed no signs of fibrosis.

Numerous inclusions were seen in the severely enlarged cells of the follicular epithelium of the thyroid gland.

A few inclusion bodies were demonstrated in the excretory ducts of the salivary glands.

The spleen showed blood forming foci, but no inclusions.

Discussion

The clinical picture of our case was in accord with earlier published cases with blood dyscrasia, jaundice, petechiae and hepatomegaly. Excellent descriptions of the morphology of the intranuclear and cytoplasmic inclusion bodies have been given by Cappel & McFarlane and by

Wyatt *et al.* Our findings agree in detail with their descriptions. We found no signs of interstitial plasmocellular pneumonia otherwise common in generalized cytomegalic inclusion disease.

The histochemical properties of the inclusions have been the subject of much research. On the basis of literature studies and personal investigations Seiffert arrived at the conclusion that fully developed intranuclear inclusions contain a large amount of desoxyribonucleic acid, while the cytoplasmic inclusions consist mainly of carbohydrates and contain only a small amount of nucleic acids. In our case the intranuclear inclusions also stained red with haematoxylin-eosin, and staining according to Feulgen demonstrated the presence of chromatin. The cytoplasmic inclusions showed up clearly in specimens stained according to McManus. Like Seiffert and unlike Lendrum, we did not

find the inclusions to stain with phloxine-tartrazine. The local distribution of the inclusion bodies in the various organs in our case was typical.

No effective therapy is available for this disease. Our patient was treated with penicillin, streptomycin, aureomycin, sterosane and cortisone without any dem-

onstrable effect. In newborns with this fulminant form of the disease the prognosis is said to be extremely gloomy, but the high frequency of latent involvement of the salivary glands observed at routine autopsy of infants suggests the existence of less serious forms of the disease.

Summary

A typical case of generalized cytomegalic inclusion disease in a newborn premature is described. The infant died at 26 days of age. The signs and post mortem findings coincided with those reported in cases on record. Antibiotics produced no demonstrable effect.

Maladie d'inclusion cytomégalye généralisée.

Description d'un cas typique de maladie d'inclusion cytomégalye généralisée chez un nouveau-né prématuré. Ce bébé est mort à l'âge de 26 jours. Les symptômes qu'il présentait ainsi que les constatations faites à l'autopsie coïncidaient avec les observations rapportées pour les cas signalés dans la littérature. Les antibiotiques sont restés sans effet apparent.

Generalisierte cytomegalische Einschlusskörperchenkrankheit.

Ein typischer Fall einer cytomegalischen Einschlusskörperchenkrankheit bei einem frühreifen Neugeborenen wird beschrieben. Das Kind starb am 26. Lebenstag. Die Symptome und Sektionsbefunde stimmten mit denen von andersorts beschriebenen Fällen überein. Antibiotika hatten keine nachweisbare Wirkung.

Inclusión citomégalya generalizada.

Se describe un caso típico de inclusión citomégalya generalizada en un recién nacido prematuro. Dicho lactante murió a los 23 días de edad. Los signos y los hallazgos autopsícos coinciden con los encontrados en otros casos relatados. Los antibióticos no produjeron efectos demostrables.

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Flensburg Children's Hospital
Malmö, Sweden (S.-I. B.)

CASE REPORT

Albright's Syndrome in a Four-Months-Old Girl

by HELENE PANDE

*From the University of Bergen, School of Medicine, Department of Pediatrics
(Head: Professor Alfred Sundal, M.D.)*

In 1937 Albright *et al.* (1, 2) described a syndrome consisting of changes in the skeleton of the type fibrous dysplasia, café-au-lait-coloured areas in the skin and precocious puberty (in females). With all the three symptoms present the condition is very characteristic and easily recognisable. It is a very rare condition, up to the present time only about 50 cases have been recorded.

Changes in the bones of the type fibrous dysplasia can also be found alone, or in some cases in connection with pigmented areas in the skin. These cases are not so rare, and are often described as "abortive" or incomplete forms of Albright's syndrome, but they scarcely deserve this designation. This should rather be used for cases which exhibit the whole classical triade. From Scandinavia one complete triade (3) and two incomplete (10, 13) are known.

Signs and Symptoms

The fibrous dysplasia in Albright's syndrome can occur from the earliest childhood and has its progression during the growing period of life. The lesions in the bones vary from one to numerous foci consisting of a rubbery, somewhat compressible tissue of greyish-white to brownish colour (16). The

changes have their source in the borders of the medullary cavity and, during progression, can fill the whole cavity or hollow out the cortex from the inside. The periost remains intact and makes way for larger expansions. Gradually the fibrous tissue becomes scattered throughout by small trabeculae of primitive, newly-formed bone tissue, and it may then feel gritty. Microscopically the pathological tissue can be seen as a finely fibrillated connective tissue with spindle-shaped, slim cells arranged in loose bundles and whorls. It is rather poor in vascularity. It may also be more collagenous with fewer and coarser cells. The border towards the normal bone-tissue is sharply defined (16).

The changes most often occur in the upper parts of the femur; after that the other long bones of the extremities, the skull and the ribs. The vertebrae are rarely affected. There is a strong tendency to unilateral and segmental distribution of the lesions. In the long bones the changes most often occur in the diaphyses, secondly the metaphyses and rarely the epiphyses. It has often been held as a characteristic that the epiphyses always went free, or that they were only affected after the epiphyseal lines were closed, but in the case referred to later, there were also affections of epiphyseal nuclei.

The values of calcium and phosphorus in serum are mostly normal, but the alkaline phosphatases are very often increased, specially in periods when the disease is in progression. At an adult age there is usually

stagnation, but relapses in connection with pregnancy have been seen. Malignant development also occurs, but that is rare (5, 13).

Roentgenographic examinations can reveal a slight general osteoporosis before the distinct lesions gradually appear as pseudocystic clarifications (8). When metaplastic bone trabeculae are formed in the fibrous tissue the clarifications appear veiled and look like smoke or ground glass (11). If the bone metaplasia predominates the areas will look sclerotic and this is especially characteristic for the base of the skull. This combination of clarified and sclerotic areas is very typical for the roentgenological picture of fibrous dysplasia.

The café-au-lait-coloured areas are mostly localised to the back, neck and scalp, and vary in number and size. Their borders are well defined, but irregular. The colour is due to an increase of melanin in the stratum basale and there are no other changes in the skin. Mostly the patches are discovered just after birth, but some authors report cases in which they were first seen when the child was several months old (6, 18, 19). Their localisation is also often unilateral and segmental, but bear no relation to the localisation of the adjacent fibrous dysplasia.

The precocious puberty in the females can often occur very early. In 14 of 35 cases reviewed by Ferrante (8), symptoms showed before the age of two. Most often it starts with a slight metrorrhagia, later to be followed by development of the breasts. It may take years before a regular cycle is established. The precocious puberty is of cerebral type and finally there will be normal maturity and reproductive ability. The quantities of 17-ketosteroids, gonadotropins and estrogens in the urine have been found normal (8, 9, 14).

Other endocrine changes: hyper- and hypo-thyroidism, acromegalic features and a few cases of precocious puberty in males, are known (7, 13, 20).

The clinical picture of the disease will be evident from the above. Large foci of fibrous tissue weaken the bones so they may bend and assume grotesque shapes. There is a

great tendency towards pathological fractures. These are mostly strikingly painless and heal well in the usual time (17). Strongly expanding foci in the costae, maxilla, skull etc. may show visible tumors (4) or symptoms of pressure on the nerves as sight or hearing-disturbances (7).

The skeletal development is most often accelerated with the result that these patients are tall as children and small as adults.

The cause of the syndrome is not known. Till now it has to be placed in the heterogeneous group of congenital anomalies of development (6, 12). Heredity has never been proved. Certain relationship between the three symptoms has not been found either. It might be reasonable to look at the endocrine disturbances as a consequence of pressure or irritation on the base of the brain from the frequently very sclerotic areas near that region. But Albright's syndrome without changes in the skull has been seen (20), as well as other cases with massive sclerosis in the region around the hypophysis, but without precocious puberty or endocrinopathies (10).

Sternberg and Joseph (18) found hyperplasia of the basophilic cells of the hypophysis in one case. As far as is known, this has not later been recorded. In another case Ferrante (8) found an EEG with signs of changes in the basal brain structures. Pray (15) reported an interesting case with arrest of the precocious puberty after an enlarged, cystic ovary was removed. He presumed that the removal did not change the underlying cause of the precocity, but simply removed an extremely sensitive endorgan. No explanation can be offered as to why this ovary reacted in a more sensitive manner than the other one. The precocious development of the skeleton continued.

The prognosis is difficult to give because the course of the disease is erratic. If the changes in the bones are great, they can show the most grotesque deformities and degrees of invalidity. The precocious puberty is a great psychical strain on the patient and those in charge of the child must be prepared and taught to take care of this

in the best way possible. In all other respects these patients show normal health and mental ability.

No treatment is known. Roentgen therapy has failed. Orthopedic surgery can be of help.

Case Report

Girl, O.E. born March 7, 1958. No. 3 of 3 siblings. Nothing contributory in the family history, especially no cases of bone affections, pigmented patches in the skin, precocious puberty or other endocrine disorders. Gestation and delivery were normal. Weight: 3000 g. Her mother had parotitis in the second week after delivery, but the child showed no symptoms. She was breastfed, had good appetite, thrived and gained weight. No icterus. In her seventh week she got an upper respiratory tract infection with fever, but recovered in a week after administration of penicillin and streptomycin.

From the second week her parents noticed several café-au-lait-coloured patches in her skin. They darkened gradually, but had constant localisation. When the child was 3 months old there were daily traces of clear, whitish mucus from the vagina. After 14 days the discharge became slightly mixed with old and fresh blood, and the child was brought to the Children Hospital, Bergen.

On admission there (July 10, 1958) she had a healthy appearance, but was somewhat thin. Length 60 cm (average for 4 months: 61 cm), weight 4880 g (average for her length: 5900 g). Turgor and muscle tone were normal, she raised her head and chest well, smiled easily and showed mental alertness for her age. Head circumference 40.5 cm (normal). No pathological signs were revealed by the ordinary, clinical examination of head, heart, lungs, abdomen, reflexes.

She had several café-au-lait-coloured, irregular patches on extensive parts of the back, the left side of the neck, the scalp and the upper part of the left arm. (Fig. 1). No hyper-pigmentation of the mucous membranes. The breasts were slightly and symmetrically enlarged. There was no pubes and no axillary hairgrowth.

Hgb. 76%. Erythr. 3.48 mill. Index: 0.96. White blood cells normal. Thrombocytes, bleeding and coagulation time normal. No pathological findings in the urine. Serologic syphilis reactions negative. ECG and EEG normal.

Serum-calcium, mg/100 ml	12.4-11.1-10.5
Serum-phosphorus, mg/100 ml	6.5- 5.1- 4.8
Alk. phosphatases,	
Bessey & Lowry units	14.5-16.0-12.2

(Bessey & Lowry units $\times 1.7$ = Bodansky units.) That is, slightly raised alkaline phosphatases.

Hormone analysis of the urine showed normal values for her age, 4-6 months. (The hormonelaboratorium, Haukeland Hospital, University of Bergen. Chief: dr. philos. K. F. Stoa.)

	23/7 γ/day	18/8 γ/day	8/9 γ/day
Estrogens (Brown)			
Estradiol	1.9	-	1.1
Estriol	1.9	-	3.5
Estrone	2.4	-	1.5
17-ketosteroids (Zimmermann/Callow)	2.6 (?)	-	0.2
17-hydroxysteroids (Gibson/Norymberski)	3.7	-	1.3
Pregnanliol (Klopper <i>et al.</i>)			0.1
Gonadotropins : < 10 mouse units/day (20/9) (Permutit adsorption)			

Gynecological examination (Aug. 28): The vaginal mucosa was rather succulent, but microscopic examination of smears revealed no signs of cornification of the epithelial cells. Portio uteri was normal, but there was some sanguinolent mucus from the cervix. Uterus was slightly enlarged, about 5 cm long and as thick as a pencil. The ovaries could not be felt.

Roentgenological examination showed a general, diffuse osteoporosis making the patterns of the normal bone structure very marked. The skeletal age corresponded to her chronological age. There were several foci of fibrous dysplasia in the bones (Fig. 2). These foci were mainly localised to the



Fig. 1. Patient at the age of 4 months. Several, irregular café-au-lait-coloured patches in the skin.

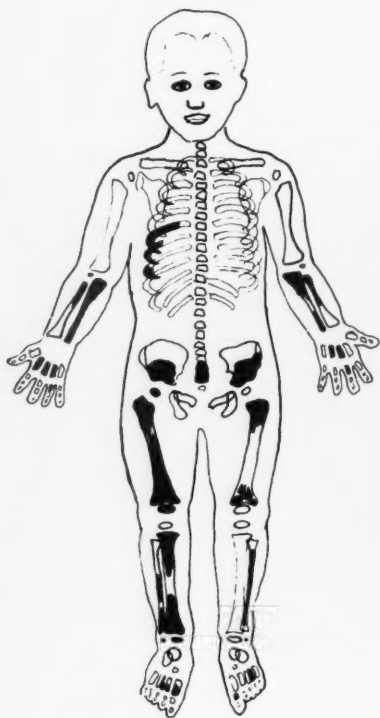


Fig. 2. The localisation of the different foci of fibrous dysplasia. No changes in the skull.

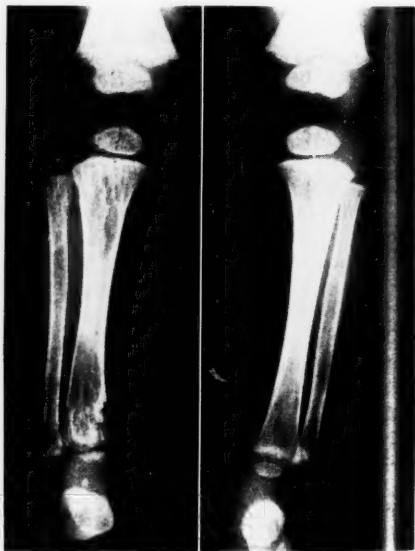


Fig. 3. Roentgenogram of the legs showing several pseudocystic clarifications, especially in the lower part of the right tibia which is deformed.

metaphyses, but several diaphyses and the proximal and distal epiphyses of the right femur were also affected. On the latter the epiphyseal lines were irregular and the metaphyseal ends looked wormeaten. The skull showed no definite changes, the sella turcica was normal.

Control of the Roentgenological findings two months later (Sept. 10) showed evident progression of the fibrous dysplasia. The distal part of the right tibia was thickened and the cortex was usurated to a thin margin on the medial side (Fig. 3.).

The child was in the hospital for two months. She got no treatment. During the first six weeks there was daily discharge of slightly sanguinolent mucus from the genital tract, this then ceased. There were no further

visible changes of the secondary signs of puberty. The child had a peculiarly "adult" look in her face.

Discussion

In this case the complete triade of Albright's syndrome was present, so no differential diagnostic problems were likely to arise. The case is of special interest because of the young age of the patient and also because of the affections of the epiphyseal nuclei. The prognosis regarding the fibrous dysplasia of the bones seems rather bad in reference to the rapid deterioration during the two months the child was under observation.

Summary

After a short review of Albright's syndrome a case in a four months old girl is reported. She showed the typical triade: (1) Several foci of fibrous dysplasia in the bones. There were affections also of epiphyseal nuclei. No changes in the skull. Two months observation revealed rapid progression of the fibrous foci. (2) Pigmented,

irregular patches in the skin. No relation to the localisation of the bone affections. (3) Pubertas praecox, indicated by slight enlargement of the breasts and sanguinolent discharge from the vagina of eight weeks duration. — The child showed no abnormal signs in any other respects.

Un syndrome d'Albright chez une fillette de quatre mois

Description d'un cas de syndrome d'Albright chez une fillette de 4 mois. Cette petite fille présentait la triologie caractéristique : 1) Foyers multiples de dysplasie fibreuse dans les os. Des noyaux épiphysaires étaient également affectés. Le crâne ne présentait aucune altération. Deux mois d'observation révélèrent une rapide progression des foyers fibreux. 2) Pigmentation de la peau en taches irrégulières. Il n'y avait aucune relation entre ces taches pigmentées et la localisation des lésions osseuses. 3) Puberté précoce, indiquée par une légère hypertrophie mammaire et des écoulements vaginaux sanguinolents qui persistèrent durant 8 semaines.

Sie wies die typische Trias auf: 1. Mehrere Herde von fibröser Dysplasie in den Knochen. Auch Epiphysenkerne waren von der Erkrankung betroffen. Keine Schädelknochenveränderungen. Zwei Monate lange Beobachtung enthüllte sehr rasches Fortschreiten der fibrösen Herde. 2. Unregelmässige Pigmentflecke in der Haut ohne örtliche Beziehung zur Lokalisation der Knochenschädigungen. 5. Pubertas praecox, angedeutet durch eine geringfügige Vergrößerung der Brüste und 8 Wochen anhaltende sanguinolente Ausscheidung aus der Vagina.

Síndrome de Albright en una niña de cuatro meses

Comunicación de un caso de síndrome de Albright en una niña de cuatro meses. La enfermita presentaba la triada típica: 1) Diversos focos de displasia fibrosa en los huesos. Los núcleos epifisarios también se hallaban afectados. El cráneo era normal. Una nueva exploración a los dos meses demostró la rápida evolución de

Albrightsches Syndrom bei einem vier Monate alten Mädchen

Mitteilung eines Falles von Albright'schem Syndrom bei einem 4 Monate alten Mädchen.

los focos de fibrosis. 2) Máculas pigmentadas irregulares en la piel, sin relación con la localización de las lesiones óseas. 3) Pubertad precoz, con ligera hipertrofia de las mamas y derrames sanguinolentos vaginales de 8 meses de duración.

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Children's Hospital
Bergen, Norway

The Iron of the Newborn Baby

by HUGH W. JOSEPHS

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and Harriet Lane Home of Johns Hopkins Hospital

There have been a number of recent papers in which important conclusions are ultimately based on a calculation of the total amount of hemoglobin or the total amount of iron with which a baby is born. Leaving the earlier attempts at calculation which were based on evidently erroneous blood volume determinations of Palmer & Lucas in 1918, there are the following:

1. Gairdner (15) *et al.*, who use the calculated total hemoglobin at birth as a basis for an estimation of the life span of fetal red cells.
2. Schulman *et al.* (40), who use figures for total hemoglobin at birth to estimate red cell life span and also to estimate the time when the baby will have used up his reserves of iron and will therefore benefit by iron medication.
3. C. A. Smith *et al.* (43), who draw conclusions regarding utilization of radioactive iron in tissue deposits acquired from the mother prenatally.
4. Josephs (25) who used calculated neonatal total iron as a base to estimate the probability of depletion later in infancy.
5. Sturgeon (44) who used total iron at birth to estimate possibility of depletion. He also used calculated total hemoglobin on which to base his estimation of total iron.

If this type of calculation is to become at all popular, it is inevitable that most of the figures for neonatal hemoglobin and blood volume will not be actually determined, but will rather be based on probability. In the case of blood volume it is obviously impossible to make determinations routinely. In the case of hemoglobin, in spite of great potential accuracy, the ordinary routine procedure is generally little more than a screening operation to exclude gross reduction in hemoglobin. It seems better to rely on a known probability than on a figure the probability of whose accuracy is completely unknown.

In the work thus far, there is considerable disagreement, and little documented information. The purpose of this paper is to supply the latter.

1. Concentration of Hemoglobin at Birth

The figures for concentration of hemoglobin at birth collected from the literature have been divided into 3 groups: cord blood, venous blood and capillary blood.

The rather wide variation in average figures obtained by different observers is

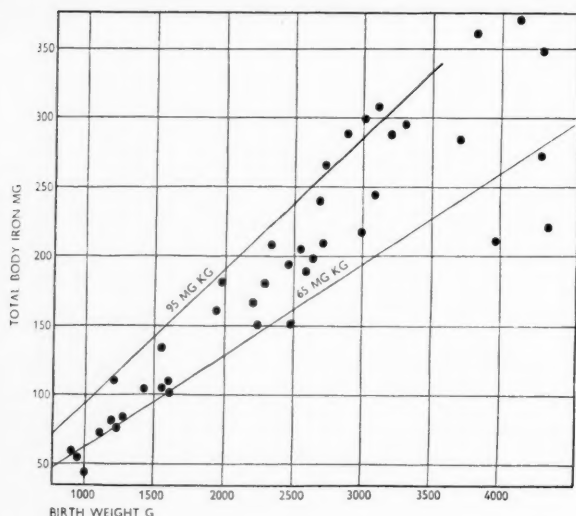


Fig. 1. Relation of total body iron to weight at birth. The chart contains the figures from the fetuses weighing less than 2000 g which are not contained in Table 3. It may be noted that in fetuses weighing close to 1000 g the figures for iron per kg tended to be lower.

probably largely a matter of technique, and standardization as well as the population being studied. However, there is a considerable fluctuation during the first day which may well be reflected in the wide scatter of the figures. In spite of these variations certain facts are clear.

Cord blood hemoglobin averages about 16 g/100 ml with many individual figures as low as 13. The hemoglobin of *venous blood* is higher averaging about 18.2 with a probable range between 16.5 and 20. An occasional figure is as low as 14. *Capillary blood* gives the highest figures averaging 20 g/100 ml with a probable variation from 18.5–22 and an occasional figure as low as 15–16 g.

At the present time there are a number of writers who use the figures for cord blood as if the difference between them and those of venous blood were negligible. There ap-

pears to be no justification for such a practice. Not only are the cord blood figures significantly lower than those of venous blood, but I can find nothing in the literature that justifies the use of cord blood for anything but a screening operation in the diagnosis of anemia of the newborn. Horvath & Hollosi (21) found a higher concentration in the umbilical artery than in the umbilical vein, and Vahlquist (45) found that within 2–7 minutes of delivery the cord blood hemoglobin was 15.9 g/100 ml, while three hours later it had risen to 16.6. At the same time venous hemoglobin had risen from 16.7 to 19.8. Also, Gairdner *et al.* (15) found an average of 17.6 g in cord blood, and later on the same day 20 g in venous blood.

Up to about 1930 capillary blood was used almost exclusively for neonatal hemoglobin determinations. Since that time there has been a gradually developed preference for venous blood as more representative of the bulk of neonatal blood. The difference between capillary and venous blood obtained at the same time has varied somewhat with

TABLE 1. Hemoglobin values at or shortly after birth.

Author	Time after birth (d = day)	No. observations	Hemoglobin		No. observations below designated figure			Method	
			Mean g/100 ml	Range	13	14	15		
A. Capillary (cutaneous) blood									
Wright & Davidson '33 (30)	1st d	17	23.4	17.5-27	0	0	0	Fe. determ.	This method gives high values
Orvath & Hollósi '35 (21)	1st d	30	18.5	—	—	—	—	Not given	
Anderson & Ortman '37 (3)	1st d	33	18.5	15-22	0	0	0	Hellige	
Waxén '37 (13)	1-12 h	16	23.2	S.D = 1.0	0	0	0	Authenrieth-Königsberg	Standardized by O ₂ capac.
Marsh <i>et al.</i> '41 (9)	$\frac{1}{2}$ -1 h	25	18.9	—	—	—	—	Sahli	
Capriro <i>et al.</i> '41 (42)	1st d	35	19.8 20.2	15-25	0	0	0		Cord tied early
Wander '44 (41)	1st d	100	21	—	0	0	0	Zeiss-Ikon	Cord tied late.
Wadley '46 (14)	1st d	12	20.2	15-25	0	0	0	Haldane	Standardized by CO method
Wittinger & Mills '49 (34)	1 h	24	20	14-24	0	0	0	Phot.-elect. colorimeter	
Wan '50 (20)	1st d	87	20.5	—	0	0	0	Haldane	
Wegberg '55 (19)	1st d	17	19.3	—	0	0	0	—	
B. Cord blood									
Wagrade & Anderson '34 (33)		40	17.1	15-20	0	0	2		
Orvath & Hollósi '35 (21)		30	15 17.2	—	—	—	—	Not given	Umbil. vein
West <i>et al.</i> '36 (18)		34	18	13-22	0	1	2	Palmer	Umbil. artery
Wough <i>et al.</i> '40 (47)		52	15.6	12-18.7	—	< 20%	—	Photoelect. colorimeter	
Marsh <i>et al.</i> '41 (9)		25	15.8	12.5-19.5	1	3	12	Sahli	
Wicks <i>et al.</i> '38 (38)		15	16	15-18.4	0	0	0	Fe. determ.	
Wmaer '45 (36)		31	17.6	15-20	0	0	1	Zeiss	
Wadley '46 (14)		11	16	13.8-18	0	1	2	Haldane	
Wollison <i>et al.</i> '51 (31)		133	16.5	13.5-19.5	—	—	—	Photoelect. colorimeter	
Wardner (15)		12	17.6						
C. Venous blood									
Wardner <i>et al.</i> '33 (17)	2nd d	30	17.2	15-18.8	0	0	0	Sahli	
Wito & Emery '33 (27)	1-2 h	31	18	14-23	0	1	3	Newcomer	
Winnard '38 (8)	1st d	20	17.2	—	—	—	—	Osgood-Haskins	
Wardner & Ortman '37 (3)	1st d	33	16.3	—	1	2	4	Hellige	
Wough <i>et al.</i> '39 (47)	2nd d	45	15.5		—	< 20%	—	Evelyn colorimeter	
Wmaer '45 (36)	4th d	31	19.4	16-22.4	—	—	—	Zeiss	
Wadley '46 (14)	1st d	15	19.8	—	0	0	0	Haldane	
Wegelius '48 (48)	immed.	77	17.8 20.8	—	1 1	7 2	9 4	Zeiss-Ikon	
Wittinger & Mills '49 (34)	1 h	24	17	14-20	0	4	8	Photoelectr. colorimeter	
Wtharto <i>et al.</i> '54 (4)	1st d	17	19.1	—	—	—	—	Visual colorimeter	

different observers. Anderson & Ortman (3) and de Marsh *et al.* (9) found no difference. Findlay (14) found slightly higher values for capillary blood but thought the difference was not significant. Vahlquist (45) found significantly higher values for capillary blood at birth, but the difference became rapidly less as the values for venous blood rose. Oettinger & Mills (34) found even greater differences which persisted for several days.

After birth, there occurs a rise in the level of hemoglobin and red count, shown especially in venous blood (14, 15, 21, 29, 34, 36, 45, 48, 50). In most of the earlier work, it was assumed that this rise was due to increased concentration as a result of dehydration after birth, and for this reason cord blood was especially valued for hemoglobin determinations. Although there is evidence that such increased concentration may in fact occur, it is coming to be believed that the rise in red cells and hemoglobin indicates also an actual increase in the total hemoglobin mass. All this is well discussed by Wegelius (48), who also suggests that the rise in hemoglobin and red cells is a reaction to a relative anoxia occurring during birth and for a short time afterwards, or until the lungs are sufficiently expanded to take care of the increased oxygen needs of extrauterine life.

The source of this possible increase in total red cell and hemoglobin mass is a subject of some discussion. In summarizing this discussion and presenting her own work, Wegelius believes that the rise is derived both from increased erythropoietic activity, and also from the release of red cell "reserves" in the spleen and elsewhere. It was also suggested that part of the increase, which occurs most prominently in venous blood, might come from

more or less immobile capillary beds. If, as Vahlquist (45) suggests from some work on animals, more than half the blood in the body at birth is present in the capillaries, then capillary hemoglobin values may have to be considered along with venous in reaching the figures to be used in calculating total hemoglobin mass at birth.

2. Blood Volume Determinations

The problem of evaluating figures for blood volume is somewhat different from that of evaluating the hemoglobin figures. In the case of the hemoglobin, the method permits a high degree of precision and, if the sample has been properly obtained, the scatter of the figures probably represents actual variations in the subjects of the investigation. In the case of blood volume, the measurement itself provides a considerable proportion of the scatter, and the actual blood volume is probably much less variable than the figures appear to indicate. For this reason, it may be desirable to use a mean figure to be applied to all cases rather than to rely on individual determinations, even when it is feasible to carry them out.

The estimation of blood volume from plasma volume and venous hematocrit, on which most of our estimations depend, has been much criticised, largely because of discrepancies between the values obtained by this method and the values obtained when plasma volume and erythrocyte volume are determined independently and combined to give the total. For adults, a factor has been determined, to be applied to the venous hematocrit when used to calculate total blood volume from plasma volume (7). Mollison *et al.* (32)

have recently shown that this factor when applied to the newborn tended to give values that were too high compared to those when red cell mass and plasma volume were determined independently.

DeMarsh *et al.* (10) with the dye method determined blood volume from 15 minutes to three hours after birth, using the sagittal sinus both for injection and later removal of blood. They found 94 ml/kg in infants whose cords were tied early, while in those whose cords were tied after separation of the placenta, they found 112 ml/kg. There was little change in the next 3 days. From the manner in which they speak of the possibility of leakage about the site of injection and the precautions they took with regard to it, one may guess that such leakage might have been a factor and that their blood volumes might be falsely high.

Ronaer (36) determined blood volume in the first few hours after birth in fifty-one newborns whose cords had been tied off before pulsations had ceased. He also used the sagittal sinus. His average figure was 91 ml/kg with a range of 75–105 in 85 percent of the cases. He also used the dye method (Evans blue).

Robinow & Hamilton (37) made their determinations on 11 babies from 1 hour to 10 days after birth, using the dye method (vital red). Their average figure was 98.3. The range was not given, but the figures were said to be "rather uniform".

Schulman *et al.* (40) studied 8 premature infants in the first eleven days of life. They used the dye method, applying Mollison *et al.*'s correction factor to their venous hematocrits, and found an average of 108 ml/kg.

Fashena *et al.* (12), using radioactive phosphorus to determine total red cell mass, studied 41 infants in the first few hours after birth. They found an average of 94.9 ml/kg for total circulating blood volume.

Mollison *et al.* (32) determined blood volume in 40 newborn infants mostly from $\frac{1}{2}$ –6 hours after birth. They determined the red cell mass with radioactive phosphorus and

the plasma volume with Evans blue, combining the two for the total blood volume, providing at the same time a factor to be applied to the venous hematocrit in order to calculate the "true" blood volume from data that included only plasma volume and venous hematocrit.

Their figure—84.5 ml/kg, with a range from about 75–95—is probably the most accurately determined value for blood volume thus far obtained. One may, however, question whether the determination as they carried it out gives the desired figure. What they determined was the circulating blood, but the time at which they made their determinations eliminates all possibility of including possible reservoirs of potentially circulating blood such as would be present in unopened capillaries or spleen. These have already been mentioned as possible source of the postnatal rise in venous hemoglobin levels.

There is another consideration. This particular method gives figures considerably below those obtained by the dye method. However, all figures for later infancy are obtained by the dye method which gives the well known figure of 76 ml/kg. If Mollison's figure is to be used in the newborn, then the later figure should be reduced to be comparable. Lately, Berlin *et al.* (35) have summarized the values for blood volume obtained by determining the red cell mass with an isotope, and then using this and the venous hematocrit to calculate the total volume. The blood volume was found to lie between 60 and 70 ml/kg. These figures give an idea of the amount by which the traditional 76 ml would have to be reduced. They do not use a factor to correct the venous hematocrit and state in their experience that a correction is unnecessary.

3. Total Hemoglobin Iron

The probable total amount of hemoglobin or of hemoglobin iron with which an infant is born, as calculated from the average hemoglobin concentration and estimated blood volume, can be given

almost any value over a wide range, depending on how one chooses the figures used for the calculation.

Using Mollison *et al.*'s blood volume figure and cord blood, Sturgeon (44) obtained 46 mg/kg as the figure for total hemoglobin iron. Using the venous blood figure of 18.2 g and Mollison *et al.*'s figure, the total hemoglobin comes to 53 mg/kg. Gairdner (15), using Mollison *et al.*'s figure and his own average cord blood hemoglobin of 17.6 g, finds 42 g total hemoglobin, or 48 mg/kg total hemoglobin iron in his standard 3 kg baby. When he used the hemoglobin of venous blood obtained later the same day, namely 20 g, the total hemoglobin came to 52 g or 57 mg/kg total hemoglobin iron.¹

Schairer & Rechenberger (39), in the course of determining the total iron content of newborn infants and fetuses, attempted to determine total hemoglobin iron by perfusing the body after death and estimating the total hemoglobin of the collected perfusion fluid. Their average figure was about 50 ml/kg with a range from 33–57. However, in these same bodies the total iron as determined by analysis of the ash came to 75 to 85 mg/kg, which, as we shall see, is about what others have found. There was therefore a considerable amount of iron unaccounted for by the iron of the hemoglobin (25–35 mg/kg). The liver and spleen together contained usually an average of not more than 7–8 mg/kg body weight, and other tissues much less. Their category of "rest" iron, amounting to as much as 15–20 mg/kg, included not only the iron in unanalyzed tissue but also the hemoglobin iron that had not appeared in the perfusion fluid—from the spleen, bone marrow, and unreachd capillary beds. The iron of unanalyzed tissue, including that of the muscles, would not have amounted to more than 7–10 mg/kg

leaving at least 5–10 mg/kg to be added to their estimated hemoglobin iron. Even in the case in which they recovered only 33 mg/kg of hemoglobin iron, the total body iron was within the normal range, suggesting either that they had failed to recover a large proportion of the hemoglobin, or else that, if the infant were anemic, the anemia was not due to external hemorrhage. In this case and in another with similarly low hemoglobin recovery, there was more iron than usual in the liver and spleen.

The average figure resulting from this procedure cannot be anything but too low if only for the reason that low figures obtained as a result of failure to wash out isolated pockets of blood could not possibly be balanced by obtaining an excess of blood in other cases. The figures have value in giving a minimum average, i.e. one which by its very existence excludes a lower figure.

The second check is an indirect one. In the first month of life the iron derived from the reduction of total hemoglobin is deposited largely in the liver and spleen. From data in the literature it is possible to determine the average amount deposited. This comes to about 50 mg, for a normal baby assumed to weigh 3.5 kg at birth with a range from 25–75 mg. At the age of one month when the total hemoglobin has about reached its minimal value, this baby should weigh about 4.2 kg and should have a hemoglobin level of about 13.5 g. From these figures his total hemoglobin iron can be calculated to be about 150 mg. When one adds the 50 mg deposited in the tissues we obtain 200 mg as representing the probable total hemoglobin iron with which the baby was born. This figure divided by 3.5 kg, his assumed birth weight, gives 58 mg as the figure for total hemoglobin iron per kg of body weight.

The average figure resulting from this type of extrapolation or "retropolation" is

¹ My own suggested figure of 68 mg/kg for total hemoglobin iron was based on a neonatal hemoglobin level of 20 g and a blood volume of 100 ml/kg. It was the result of insufficient reading and is evidently too high for a general average. As a matter of fact in the paper in which it was given, it was used only in the attempt to furnish an alternate method in the determination of the total iron of the newborn baby, and for this purpose was given relatively little weight compared with the direct determination of total iron.

useful in the same way as is that derived from the perfusion studies. It should be noted, however, that these figures were obtained from autopsy material, and although there is no reason to believe that the samples were not well freed of blood we do not know the hemoglobin levels at the time of death. On the other hand, if only the minimal amount of 25 mg had been deposited in the tissues of our "standard" baby the calculation would still give a figure of 52.5 mg/kg. This check therefore suggests that the average figure is not likely to be below 52.5.

4. Storage Iron

Storage iron was historically an important category, and much work was expended on the endeavor to determine the amount of iron in storage and the conditions under which it might vary. Although Gladstone in 1932 (38) showed clearly that, if one eliminated the effect of the presence of blood, the tissues contained relatively little iron, it was not until after 1940 that this fact came to be generally recognized, and that the reserves of iron with which the child was born were to be found for the most part in the hemoglobin, whether circulating or stagnating in congested tissues.

Table 2 contains the available figures appearing since 1930. Only the iron from liver or liver and spleen is included. In general, other tissues contain much less iron and the majority of it is in a form not available for general use. The only tissue containing significant amounts of potentially available iron not included in the table is the bone marrow. How much this amounts to is unknown.

The results of Adler & Adler and of Iob & Swanson show the effect of failure to eliminate hemoglobin iron, although Adler & Adler attempted to do so by washing the tissue

before analysis. Gladstone determined the hemoglobin in a small sample, and calculated the amount of iron to be subtracted from the total determined on a second sample. The increased error due to this procedure is shown in the greater "scatter" of his results, but his averages indicate that his method was effective. In all the other analyses, the tissue iron was freed of virtually all blood, or the iron was "extracted" from the tissue in such a way as to avoid including hemoglobin.

The average figure from the tables amounting to 7-8 mg/kg should be increased somewhat to take care of iron not included in the recorded analyses, especially that of the bone marrow. How much this should be is not known, but would probably not amount to more than 2-3 mg/kg, bringing the average figure for storage iron at birth to about 10 mg/kg. The range for this figure is fairly large—from 3-4 to 12-16 mg/kg.

5. Functional Tissue Iron

The figure used for this category of tissue iron has been derived in a number of ways. An earlier figure was based on the irreducible minimum concentration of tissue iron present in growing rats during development of iron deficiency anemia. This amounts to 5 mg/kg (24). A more recent figure, derived from observations of Venn & McCance, is 7.5 mg/kg (46). That amount represents iron taken by the tissues in rapidly growing anemic pigs given a not excessive amount of iron, on the assumption that normal tissues would take what they needed, but no more, in the presence of maximal hemoglobin demand. Sturgeon's figure (44), based on the probable amount of myoglobin in muscle and the probable muscle mass varies with the age of the infant. His figure is 4 mg/kg body weight at birth, but becomes higher later as muscle mass increases and becomes richer in myoglobin. However, this figure should be increased by the amount of iron in the heme enzymes.

For an approximation of the amount in heme enzymes we must turn to analyses of animal tissues. When rats were depleted of their iron during growth the amount of iron

TABLE 2. *Iron content of liver or liver and spleen.*

Author	Number of observations	Wt. of infant kg	Iron content of liver and spleen			Remarks
			Mg per 100 g fresh tissue	Total	Mg per kg body weight	
Adler & Adler '32 (1)	6	varied	57 43-74		15-25 ^a	Includes premature babies. Liver slices washed to remove blood
Iob & Svanson '34 (23)	7	varied	54 ±	30-120	8.8-40 ^a	Mostly premature babies. No attempt to remove blood.
Gladstone '32 (16)	5	1.0-2.0	21	—	5-7	Figures for liver only. Hemoglobin content of tissue determined separately and subtracted from the total.
	4	2.0-3.0	20 ±	—	10 ±	
	5	above 3.0	21.6	48 20-70	11.8	
Brückman & Zondek '39 (6)	4	not given	35	—	13 ^a	Tissues extracted in a manner to exclude hemoglobin. Iron of spleen included.
Lintzel <i>et al.</i> '44 (28)	4	7-8 m	—	—	6	Whole body or individual organs perfused to remove blood.
	7	8-9 m	—	—	7.5	
	7	Av. 3.6	20 ±	—	8 ±	
Renaer '45 (36)	7	not given	10.9		3-4	Figures for liver only. Tissues extracted in a manner to exclude hemoglobin.
Schairer & Rechenberger '49 (39)		1.22	—	6.2	5.1	Whole body or individual organs perfused to remove blood. Non-hemoglobin iron of spleen included in these figures.
		1.42	—	17.3	12.2	
		1.98	—	7.1	3.6	
		3.0	—	36	12.0	
		3.2	—	29	9.2	
		4.0	—	19	4.6	
Widdowson & Spray '51 (49)		4.3	—	18	4.1	Figures for liver only.
		1.97	20	12-16	6-8 ^a	
		2.29	20	13-17	6-8	
		3.1	37	35-50	12-16	
		3.1	25.5	20-30	7-9	
		3.1	10.4	10-12	3-4	
		4.0	21.1	25-30	6-8	
		4.4	16.7	25-30	5-7	

^a These figures are calculated on the assumption that the weight of liver is 3-4 % of the body weight.

Note: The greater part of this iron is in the liver and figures for mg per 100 g fresh tissue refer to the liver only. The iron of the spleen when it is known has been added to the total and storage iron per kg of body wt has been calculated from this total figure.

in the tissues reached an irreducible minimum considered to represent the heme enzymes. In such rats the irreducible minimum in blood-free liver tissue was found to be about 1.5 mg/kg of body weight, and

in the muscles about 5 mg/kg (26). While these figures may not be strictly applicable to newborn infants they give some idea of the relative amounts of functional iron in liver and muscles.

TABLE 3. *Total body iron at birth.*

In order to shorten the table, all individual determinations in subjects weighing less than 2000 g at birth were omitted. They have, however, been included in making up the average figures for total iron/kg and are included in the chart.

Name	Birth weight kg	Total iron mg	Total iron per kg mg	Average of total iron	Number in series	
Hugounenq 1899(22)	2.72 3.30	268 295	98 89		5	
Iob & Swanson (23)	2.25 2.91	152 284	68 97	75	8	
Schairer & Rechenberger (39)	2.72 3.0 3.2 3.75 4.28 4.30	211 217 284 284 272 347	77 72 88.7 76 65 81	81.5	9	Placenta previa
Schairer & Rechenberger series 2 (39)	4.11 2.68 2.64 2.47 2.90 2.35 2.58 2.23	372 152 197 193 242 208 205 168	79.5 61 74 79 83.5 88 79.6 75	77.5	8	The infants in this series had lived for 8-21 days
Widdowson & Spray (49)	1.96 2.30 2.60 3.08 3.05 3.10 3.85 3.97 4.37	160 180 190 245 300 315 360 210 220	81 78 73 79.5 98 101 95 53 51	76	11	Placenta previa

6. Total Body Iron

The numerous determinations gathered from the literature are contained in Table 3, and have been charted in Fig. 1. The method comprised the ashing of the entire body and determination of iron in the ash. However, both Schairer & Rechenberger and Widdowson & Spray analyzed certain tissues separately, later reincorporating the results into the total.

Hugounenq's figures have historical interest, but apart from that, they were obtained with the utmost care and atten-

tion to all "possible" errors, even though the method was not especially suited to biological work. Iob & Swanson do not give the source of their material, so that one has no inkling regarding the condition of the mother or the cause of death. They analyzed only one baby that was not prematurely born. The figures both of Schairer & Rechenberger and of Widdowson & Spray require no comment regarding the manner in which the work was done. The second series of Schairer & Rechenberger, while not strictly newborn, is in-

cluded because in the three weeks span of life there would be no gain or loss of total iron, although there would probably be a shift from hemoglobin to tissues.

There are three low figures in the work of these two groups that may be singled out for comment. Two of them were from somewhat overweight infants born after placenta previa. Although it is ordinarily assumed that in placenta previa the bleeding is entirely from the maternal side of the placenta, these two figures suggest that the infant might suffer some loss of iron. The fact that placenta previa occurs once in about 200 pregnancies and that generally the infant cannot be delivered alive makes it unnecessary to consider this a probable cause of later iron depletion in the baby. On the other hand, it might be well to remove such cases from consideration in obtaining an average figure and range of values to be applied to living newborn babies for calculation of later probability of depletion.

A third low figure, close to 50 mg/kg, in Widdowson & Spray's series, came from an overweight infant with hydrocephalus. It is unlikely that the amount of fluid in the hydrocephalus would be sufficient to influence the results, but the amount of fat in this baby was especially high—about 1000 g more than was present in a baby of 3.0 kg birth weight. The authors remark on the great increase in fat that occurs in the newborn as birth weight increases above 3000 g. If one subtracts the extra fat, which contains no iron, from the total weight of this baby, it is evident that the iron per kg would be much higher than appears on the chart—67 instead of 50. As in the case of placenta previa, this is an exceptional infant, and should be treated as such in judging the probability of low figures for total iron in the newborn.

With the figure for total iron, which is perhaps the most clearly acceptable figure that we have, we can offer another check on the value for total hemoglobin iron, by

TABLE 4. *Figures for total hemoglobin iron obtained in different ways.*

Method	Total hgb. iron mg/kg
Cord blood hgb. 16.2 g. Blood vol. 84.5	46
Cord & venous blood hgb. 17.5. Blood vol. 84.5	50.5
Venous blood hgb. 18.3. Blood vol. 84.5	52.5
Venous & capillary combined hgb. 19.3. Blood vol. 84.5	55.5 ^a
Venous & Capillary blood combined. Blood vol. 90	59 ^b
Analysis of postmortem perfusion	< 50.5 ^c
Calculated total hgb. iron at month plus iron deposited in tissues	58 ^d 52-64
Total hemoglobin iron (by analysis) minus probable iron of tissues	60 55-67
Based on C. A. Smith <i>et al.</i> 's data on maximum circulating radio activity in 1st six months	54-64

^a Based on the assumption that the capillaries contain a significant proportion of total blood.

^b Based on possibility that blood vol. at birth will be somewhat increased in the next day or two.

^c No figure obtained by this method, could be anything but low.

^d The method is subject to criticism but the minimum has value as lower limit of probability.

subtracting from 78 the probable figure for tissue iron, amounting to 17.5 mg/kg, with variation from 11-23. That would give 60 mg/kg with a probable range from 55-67 mg.

Discussion

The figures for total hemoglobin iron obtained by various means have been summarized in Table 4. From what was said earlier, it may be doubted that cord blood is suitable for calculating the total hemoglobin. Actually there is a double error associated with its use:— not only is

it not representative of the circulating blood of the infant, but, because of the low hematocrit figure, the value for blood volume will also be below what it would be were it based on the hematocrit of venous blood later the same day. From the "table of mean values" in Gairdner *et al.*'s article (15) the blood volume can be easily found, by dividing the total hemoglobin by the hemoglobin concentration. It rises from 238 ml at birth to 265 ml later on the first day, a result due solely to the lower value for blood volume per kg resulting from the lower hematocrit value.

C. A. Smith *et al.* (43) in their study of radioactive iron acquired transplacentally also use Mollison's equations applied to their own carefully obtained data. They used cord blood for hemoglobin determination and obtained figures for total hemoglobin iron varying from 40–60 mg/kg. Later on, at about 6 months of age many of the infants showed a higher content of radioactivity in their circulation than was present at birth. This was interpreted to mean a transfer of iron from stores present at birth to the hemoglobin. They found further that those babies with the lowest circulating hemoglobin at birth had the greatest later increase in total circulating radioactivity and therefore "seemed to have relatively large amounts of stored iron at birth". Now this result could have two interpretations:—it might be an "artefact" due to the calculation of total hemoglobin at birth resulting in a figure for hemoglobin lower than the actual one, or the low hemoglobin value might have been the result of antenatal hemolyses.

If one now takes in each case the maximum value for hemoglobin containing the transplacental radioactive iron, multiplies

it by 3.4 and divides by the birth weight one will obtain a figure representing the iron per kilogram which must have been present at birth in the hemoglobin as well as that portion of the tissue iron that will later be used for hemoglobin. The average of all these figures is 64 mg/kg. Since the functional iron has a relatively slow turnover rate (11), the iron present at birth that can later be used for hemoglobin can come only from the birth "stores" which as we have seen ordinarily amount to about 10 mg/kg (with a maximum value of 16) and which will have to be shared with the growing tissues. From this work, then, we have a range from about 54 mg/kg to 64 mg/kg, the lower figure based on maximum use of tissue iron to supplement the low levels of hemoglobin iron at birth, the higher figure a maximum based on the possibility that all the radioactive iron eventually used in hemoglobin was in the hemoglobin at birth, but was missed because of "error" in the factors used in the calculation.

From the recorded experimental figures and the various "checks", we can gain some idea of the limits within which the total iron and the hemoglobin iron are likely to vary. The figures for total iron are the simple result of analysis. There are only a few cases about which there might be reservations and these have been discussed. In the case of hemoglobin iron, there will probably be no agreement. If an average figure is used, the indications are that it should be above 52 mg/kg at the very least. The two checks derived respectively from the observed figures for total iron and tissue iron, and from C. A. Smith *et al.*'s observations on transplacental iron, indicate an average from 58–60 mg/kg with a range from about 54 to 65.

In certain types of study in which one is dealing with numbers of cases of a uniform population treated on a statistical basis or when one is dealing with a probability or prediction based on total hemoglobin or hemoglobin iron at birth, a figure derived in the fashion of the one above is probably as satisfactory as it is possible to obtain. However, in many cases in which the hemoglobin has been properly and accurately determined it might be desirable to calculate the total hemoglobin iron with the use of a figure for blood volume. In most cases this would mean all the hemoglobin with which the baby is born, and not merely that which is circulating within the first few hours.¹ Gairdner *et al.*'s figures, showing as much as a twenty-five percent increase during the first day, are largely but not entirely the result of the difference between cord and venous blood. Some of the difference may represent an actual increase in the amount of circulating hemoglobin. To the extent that this increase comes from unopened capillary beds or other possible "reservoirs" of non-circulating blood, the figures given by Mollison *et al.* will fall short of the figure needed to calculate total hemoglobin.

One has two obvious choices:— one is to add an arbitrary figure to Mollison *et al.*'s 84.5 ml/kg depending on what one thinks is the probable discrepancy, the other is to use the published figure and note that it may be giving low values and modify one's conclusions accordingly. The figures in Table 4 give an approximation

of the amount of total hemoglobin iron per kg reached as the result of using different sites from which to obtain blood. To reach the average of 58–60 mg/kg indicated by the observations on total iron as well as those by C. A. Smith *et al.* would require a blood volume of 90 ml/kg.

There has been no attempt in this paper to discuss the probability of abnormal figures for total iron. Actually little is known on the subject. Recent observations indicate that the older teaching based on the studies of McKay and of Strauss, that anemia in the mother had no bearing on the neonatal hemoglobin level, is not correct. Albers (2) found a clear correlation between the presence of a maternal hemoglobin level below 10 g/100 ml and a reduced hemoglobin level in the baby, which could be prevented by treatment of the mother in the latter part of pregnancy. More recently, Hagberg & Lundström (19) have found that intravenous iron, given to normal mothers in the latter half of pregnancy, raised the average neonatal hemoglobin level by as much as 2 g/100 ml.

However, the possibility that an increase or decrease in the availability of maternal iron may influence neonatal hemoglobin is only one aspect of prenatal care, and it may be time to reexamine the basis for the statement often made dogmatically and without documentation that the condition of the mother has no demonstrable relation to the hemoglobin of the baby. It might be borne in mind that a reduction of hemoglobin from 20 to 17 g

¹ If the total hemoglobin is to be calculated individually from the observed hemoglobin level, it should be realized that a low level of hemoglobin at birth may not mean loss of iron or a lowering of the total iron content. From Schairer & Rechenberger's experience and, even more, from that of C. A. Smith *et al.*, a low neonatal hemoglobin level was more likely to be associated with increased storage, thereby indicating possible antenatal hemolysis, than with a reduction of total iron.

may not show up in a statistical series. It represents about 25 mg of total hemoglobin iron or 8 mg/kg. At one year of age, it is equivalent to a reduction in hemoglobin of little more than 1 g/100 ml. These are small figures to be concerned

about from a practical clinical point of view; from the point of view of our understanding of the factors that influence hemoglobin and iron metabolism in infancy, their importance is out of proportion to their size.

Summary

In this paper the author has examined the basis for the figures used in determining or calculating the iron present in the newborn baby, both the total body iron and that combined with the hemoglobin. It is impossible to state the results in the form of definite conclusions but the following suggestions may be made.

1. Cord blood is not suited for determination of neonatal hemoglobin when the purpose is to calculate the total iron of the newborn baby.
2. Blood volume determined within the first few hours of birth may have to be corrected upward to take account of unopened or stagnant capillary beds or other sections of the circulation not included in the measurement.
3. A low neonatal hemoglobin level is far more likely to be due to hemolysis with conservation of iron than to hemorrhage with consequent loss.
4. From an analysis of the various figures, the total iron was found to average 78 mg/kg with range from 65-90. The total hemoglobin iron is more problematical. The author accepts the figure, 60 mg/kg, to be used in his own work. Reasons are given for rejecting an average figure below 52 mg/kg.
5. On the basis of the origin of the infants used in much of this study it is felt that the figures as given would tend to be rather low, and that in the case of infants belonging to better socio-economic classes the figures might well be considerably higher.

Le fer chez le nouveau-né.

L'auteur a étudié les bases à prendre pour les chiffres utilisés dans le dosage ou le calcul des quantités de fer présentes chez le nouveau-né et cela tant en ce qui concerne le fer total de l'organisme que le fer combiné avec l'hémoglobine. Il est impossible de traduire les résultats de cette étude sous la forme de conclusions définitives, mais les suggestions suivantes peuvent être faites : 1) Le sang du cordon ne convient pas pour le dosage de l'hémoglobine chez le nouveau-né si ce dosage est effectué en vue de calculer la quantité totale de fer présente chez ce nouveau-né. 2) Il arrive que le volume du sang déterminé au cours des premières heures qui suivent la naissance doive être corrigé dans le sens positif pour tenir compte des réseaux capillaires non encore ouverts ou stagnants ainsi que d'autres secteurs de la circulation non compris dans le calcul. 3) Il est fort probable qu'une insuffisance du taux d'hémoglobine chez le nouveau-né est plutôt due à un processus d'hémolyse avec conservation du fer qu'à une hémorragie ayant entraîné des pertes. 4) Une analyse des différents chiffres obtenus a révélé que la concentration du fer total s'élevait en moyenne à 78 mg/kg avec des extrêmes de 65 et de 90 mg. La concentration totale du fer combiné à l'hémoglobine est plus problématique. L'auteur admet le chiffre de 60 mg/kg pour son travail. Il expose d'autre part diverses raisons qui justifient le rejet d'un chiffre moyen qui serait inférieur à 52 mg/kg. 5) En se basant sur l'origine des bébés constituant la majorité des sujets examinés au cours de cette étude, on a l'impression que les chiffres donnés tendent à être plutôt faibles et que pour des bébés appartenant à des classes jouissant d'une meilleure situation économique et sociale, ces chiffres seraient sans doute beaucoup plus élevés.

Das Eisen beim Neugeborenen.

Verfasser untersucht die Grundlage für die Zahlen, die bei der Bestimmung oder Berechnung des beim Neugeborenen vorhandenen Eisens verwendet werden, und zwar sowohl hinsichtlich des gesamten Körper- als auch des an das Hämoglobin gebundenen Eisens. Es ist unmöglich, die Ergebnisse in der Form von definitiven Schlussfolgerungen niederzulegen, aber die folgenden Anregungen können gemacht werden: 1) Nabelschnurblut eignet sich zur Bestimmung des neonatalen Hämoglobins nicht, wenn man beabsichtigt, das Gesamteisen des Neugeborenen zu berechnen. 2) Das in den ersten Stunden nach der Geburt bestimmte Blutvolumen muss aufwärts korrigiert werden, um ungeöffnete oder stagnierende Kapillarbette oder andere bei der Messung nicht berücksichtigte Abschnitte des Kreislaufs in Betracht zu ziehen. 3) Es ist wahrscheinlicher, dass ein niedriger neonataler Hämoglobinspiegel durch Hämolyse mit Erhaltung des Eisens als durch Blutung mit Eisenverlust bedingt ist. 4) Aus einer Analyse verschiedener Werte wurde gefunden, dass das Gesamteisen durchschnittlich 78 mg/kg mit einer Schwankungsbreite von 65–90 beträgt. Das gesamte Hämoglobineisen ist mehr problematisch. Der Verfasser nimmt die Zahl 60 mg/kg an und verwendet sie in seinen Arbeiten. Die Gründe für die Zurückweisung einer Durchschnittszahl unter 52 mg/kg werden angegeben. 5) Wenn man die Herkunft der in der Studie meistens benutzten Kinder in Betracht zieht, so hat man den Eindruck, dass die Zahlen zu niedrig sind und dass, wenn Kinder aus besseren sozial-ökonomischen Kreisen zur Untersuchung kämen, diese beträchtlich höher ausfallen würden.

El hierro en el recién nacido.

El autor ha examinado las bases en que se apoyan las cifras utilizadas para determinar o calcular el hierro en el recién nacido, tanto el hierro corporal total, como aquel combinado con la hemoglobina. Es imposible establecer los resultados bajo forma de conclusiones definitivas, pero pueden ser hechas las siguientes sugerencias: 1) La sangre del cordón umbilical no es adecuada para la determinación de la hemoglobina cuando el propósito sea el cálculo del hierro total del recién nacido. 2) El volumen sanguíneo determinado dentro de las primeras horas de vida debe ser corregido considerando los lechos capilares no abiertos o estásicos o otros sectores circulatorios no incluidos en la determinación. 3) Un bajo nivel de hemoglobina neonatal es más verosimilmente debido a hemólisis con conservación del hierro que a hemorragia con la pérdida consiguiente. 4) Del análisis de las diferentes cifras se deduce un valor medio de 78 mg/kg para el hierro total, con valores extremos de 65–90. Los valores para el hierro ligado a la hemoglobina son más problemáticos. El autor acepta una cifra de 60 mg/kg para ser utilizada en su propio trabajo. Se dan razones por las que se rechazan cifras medias por debajo de 52 mg/kg. 5) Debido a la condición económica de los niños utilizados en este estudio se piensa que las cifras dadas son bastante bajas y que en caso de niños pertenecientes a clases económicamente superiores los valores deberán ser sensiblemente más altos.

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Dept. of Pediatrics
The Johns Hopkins Hospital
Baltimore 5, Md.
U.S.A.

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BOOK REVIEW

Die pränatalen Infektionen des Menschen unter besonderer Berücksichtigung von Pathogenese und Immunologie: Dr Heinz Flamm, Vienna.

Georg Thieme Verlag, Stuttgart 1959, price 19: 50 RM.

Prenatal infection in man has in recent years attracted increasing attention from many aspects. It is therefore extremely valuable that the Institute of Hygiene at the University of Vienna through Dr. Heinz Flamm now has presented extensive studies of the literature together with some personal work, including experimental investigations, on this important subject.

The largest chapter is devoted to prenatal virus infections. Dr Flamm specially discusses the dermatotropic and neurotropic virus infections. Concerning the important question of the effect of rubella on the foetus highly detailed data are given. In Dr Flamm's opinion, rubella in the first trimester of pregnancy, and possibly shortly before conception, entails risk of congenital malformation. He advises prophylactic administration of serum when there has been direct contact with rubella before the 16th week of pregnancy; the serum should be given before the fifth day of the incubation period. By this means the morbidity is believed to be reducible from 10 to 1 per cent. The risk of serious foetal maldevelopment from rubella is estimated to be about 20 per cent. The indications for inducing abortion are discussed on the basis of this figure, but no categorical statement is expressed and no clear standpoint is taken. That many other virus infections probably can give rise to similar foetal maldevelopment is also pointed out.

The risk of contracting poliomyelitis during pregnancy is discussed at length. From the literature Dr Flamm has calculated a considerable excess of morbidity from this disease in pregnant women. He believes that intra-uterine infection of the foetus with poliomyelitis definitely may occur. A detailed account is given of "Die generalisierte Einschlusskörperchen-Nekrose", which seems largely to correspond to the congenital herpetic infection that has been reported also from Sweden. Combination of such conditions with staphylococcal infection is not discussed, however. The rarity of epidemic hepatitis and serum hepatitis in pregnancy is pointed out.

A special chapter deals with immunology during the prenatal and neonatal periods. From the opinions here reviewed it is natural that Dr Flamm should consider vaccination against smallpox or with other live viruses to be contraindicated during early as well as late periods of pregnancy. Investigations of Woodruff, Burnet & Fenner are cited to support the opinion that vaccination of the mother, and thereby conveyance of antibodies to the foetus, may lead to impairment of the infant's ability to produce antibodies during the neonatal period. The infant of a vaccinated mother may be expected to possess at birth passive homologous immunity whose titre at least equals that in the mother at the same time. Nothing is mentioned of differentiation of antibodies in this respect. Concerning the importance of this passive immunity for the ability to produce antibodies in the first year of life, Dr Flamm expresses complete agreement with the opinion held by Vahlquist and his co-workers, i.e., that the apparently poor antibody-producing capacity of infants is attributable partly to the influence of passive immunity

and partly to low immunogenic experience. The good results of vaccination in early infancy, however, show that even infants can produce antibodies.

Concerning toxoplasmosis Dr Flamm strongly believes that only recent disease may involve risk to the foetus. A woman who has had one toxoplasmotic child, there-

fore, need not fear repetition in subsequent pregnancies.

The book has an extremely comprehensive list of references. Those who penetrate the book thoroughly will be amply rewarded, but brief summaries of results and conclusions would possibly have constituted an additional asset.

Hans Ericsson, Stockholm

Acta Paediatrica 48: July 1959

ANNOUNCEMENT

First international Medical Conference on Mental Retardation

The First International Medical Conference on Mental Retardation, organized by the Maine chapter of the American Academy of Pediatrics, the Division of Maternal and Child Health, Maine Department of Health and Welfare, and the Pineland Hospital and Training School, Pownal, Maine, will be held from July 27 through July 31, 1959, at the Eastland Hotel, Portland, Maine. The program will include in its five days of general sessions addresses on Brain anatomy, the reticular system, head anomalies, phenylketonuria, lipoids, birth injury, embryology, infections, mongolism, erythroblastosis, ther-

apy, psychiatry, psychology, behavior disorders, and the like, by outstanding authorities on these subjects. Not intended to answer all questions on the problems concerning mental retardation but rather to construct the problems which have to be attacked scientifically, the Conference is open to all physicians throughout the United States, Canada, and other countries of the world—following immediately after the International Pediatric Congress at Montreal, Canada. Further information can be received from Dr. Ella Langer, Chairman of the Arrangements Committee, State of Maine Department of Health and Welfare, Augusta, Maine, U.S.A.

From the Pediatric Clinic, Kronprinsessan Lovisas Barnsjukhus (KLB), Karolinska Institutet, Stockholm, Sweden (Head: Professor C. Gyllenswärd, M.D.)

Non-lipid Histiocytosis (Systemic Reticuloendothelial Granuloma)

by GÖRAN STERKY, Stockholm

Some years ago the term non-lipid histiocytosis was introduced by Lichtenstein (12) to denote eosinophilic granuloma, Hand-Schüller-Christian's disease and Letterer-Siwe's disease. The relationship between these diseases has been a matter of much discussion (2, 3, 14, 23). Nowadays the majority of clinicians and pathologists agree that the three diseases are only manifestations of one and the same basic disorder, viz., a disturbance in the metabolism of the reticuloendothelial cells of unknown etiology.

Recent literature on the subject contains several cases which show transitional forms between the different types. In favour of a common etiology are also the cases which will be reported here. These cases show some early symptoms which do not seem to be sufficiently noted in the literature but which are of importance to the clinician. An early diagnosis may facilitate the study of the pathogenesis of non-lipid histiocytosis. Moore (15) pointed out the diagnostic value of skin smears, and this method has been applied in four of the present cases. In two of them the possibility of treating non-lipid histio-

cytosis with radioactive gold has been investigated.

According to Westling *et al.* (24) the number of cases reported in the literature does not amount to more than about 400. This figure is probably too low, considering that the pediatric literature alone comprises numerous case reports. Since 1953 six cases have been seen in this Hospital.

Case histories

CASE 1. (Boy.) Eczema on back and in auditory canal at 3 mo. At 15 mo. lymphadenopathy and local fluctuation in the neck. A defect in the occipital bone was found. Rest of skeleton normal. Biopsy of skin showed Letterer-Siwe's disease. Very good result of prednisolone and local irradiation. Check up showed small cyst in the pelvis. In good general condition at 2 yr. and 5 mo.

CASE 2. (Girl.) Inguinal eczema at 5 mo., in auditory canal and capillitium at 12 mo. Diabetes insipidus at 2 yr., when slight lymphadenopathy and severe eczema was found. Biopsy of skin showed Letterer-Siwe's disease. Pitressin with varying effect. Irradiation of temporal bone. At 4 yr. and 8 mo. in rather good condition.

CASE 3. (Boy.) Eczema in ^{HAIR (SCALP)}capillitium at 5 mo., in auditory canal at 9 mo., when severe eczema, lymphadenopathy and pul-

monary involvement was found. X-ray of skeleton at that time normal. Biopsy of skin showed Letterer-Siwe's disease. Fairly good effect of prednisolone. Destruction in vertebra and skull at 15 mo. Therapy with local and general X-ray. Died at 2 yr. and 2 mo. Necropsy showed Letterer-Siwe's disease.

CASE 4. (Girl.) Eczema in auditory canal at 9 mo. Necrosis in one tonsil at 11 mo., when eczema in capillitium, lymphadenopathy, slight hepatomegaly and pulmonary involvement was found. Normal X-ray of skeleton. Biopsy of tonsil and lymphnode showed Letterer-Siwe's disease. Respiratory distress. Cortisone in 3 days without effect. Died at 13 mo. Necropsy showed Hand-Schüller-Christian's disease.

CASE 5. (Boy.) Eczema on back and capillitium at 12 mo., in auditory canal at 17 mo. Involvement of skeleton at that time. Biopsy of lymphnode showed Hand-Schüller-Christian's disease. Irradiation without effect. Very good result of prednisolone. Lymphadenopathy and splenomegaly at 2 yr. and 6 mo. Pulmonary involvement at 2 yr. 8 mo. General and local irradiation. Respiratory distress. Died at 2 yr. and 10 mo. Necropsy showed Letterer-Siwe's disease and cor pulmonale.

CASE 6. (Boy.) Eczema in auditory canal at 12 mo. Bilat. otitis media at the same time. Eczema in capillitium at 14 mo. In the following year several times treated at ear departments. Diabetes insipidus at 2 yr. and 6 mo. A thorough investigation was then negative. Pitressin with varying effect. Biopsy of skin at 4 yr. showed Letterer-Siwe's disease. In excellent condition at 5 yr. and 3 mo. (All cases are full-term children.)

Comment

All cases began with a seborrheic eczema of ordinary appearance. In an early phase there was found eczema in the auditory canals, refractory to therapy. Thus, not only the pediatrician but also the otologist and dermatologist should have their attention directed to these early changes. Al-

though these specialists (4, 18, 19) are, in some measure, interested in such cases, they are mostly concerned with the more advanced forms of the disease.

It is believed that the youngest patients usually acquire the most malignant form of the disease. It is worth noting that the two children, with the earliest onset of symptoms, are still alive. This indicates that other factors may influence the course of the disease. Three of the reported children (Cases 3, 4 and 5) died and showed at autopsy cor pulmonale and severe pulmonary changes of the well-known type (20). Thus, it appears that early X-ray manifestation of pulmonary involvement is a bad prognostic sign.

The case reports reveal that the disease manifests itself as variable types in one and the same patient. The biopsy findings and the clinical picture are not always correlated. These facts seem to point to a common etiology.

A close relationship between monocytes and histiocytes has been suggested by many authors. One case has been reported (7) which suffered from Letterer-Siwe's disease and died in monocytic leucemia. Thus, it is interesting that monocytosis in the peripheral blood occurred in 3 of the cases reported here (Table 1). The presence of monocytosis may be of some diagnostic value.

Patients with non-lipid histiocytosis have been considered especially susceptible to infection. Hypogammaglobulinemia has some relation to antibody production and resistance to infection. No significant quantitative abnormalities of the serum proteins, particularly not of the globulin fractions have been found among these cases (Table 1). Silver *et al* (21) has not

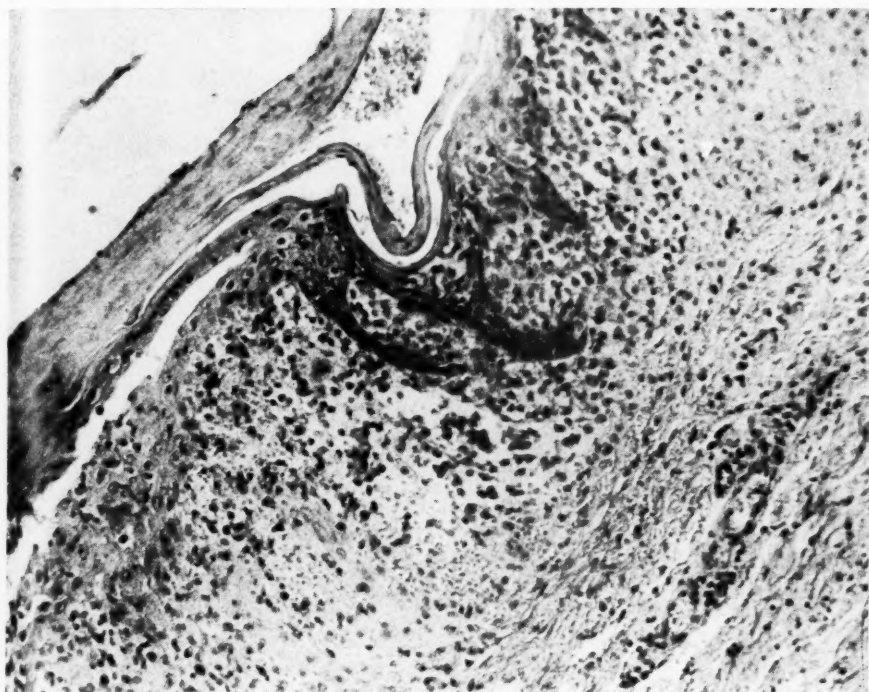


Fig. 1. Biopsy from the capillitium. Macroscopically, patch of "seborrheic eczema". Microscopically, subepidermal infiltrate of mostly histiocytes and sprinkle of leucocytes with a moderate number of eosinophiles. In the histiocytes sudanophilic fat. Infiltration with histiocytes in the epidermis and in the keratotic layers. Ulcerations in other parts. Degenerative changes in the corium.

been able to show any correlation between the production of antibodies, the pattern of serum proteins and the frequency of infections in patients with acute leucemia.

In the preliminary stage one may encounter many obstacles in differential diagnosis, but in the advanced cases the clinical picture is characteristic. Apart from X-ray, biopsy of skin (Figs. 1, 2) or lymphnodes are our best diagnostic aids. In the modern diagnosis of cancer the use of contact smear has been found very valuable, especially in detecting early sign of malignancy. The method proposed

by Moore (15) has been employed in 4 cases, and cells typical of non-lipid histiocytosis could be demonstrated in all of them (Fig. 3). This method may be a valuable screening test in seborrheic eczema, refractory to treatment.

Regarding the therapy, irradiation of whole body and local foci has been used with good results. In recent years cortisone or similar steroids have been used by several authors (1, 6, 10, 11, 16) with favourable results, which is also confirmed by the present cases. When the steroid therapy was withdrawn, the general con-

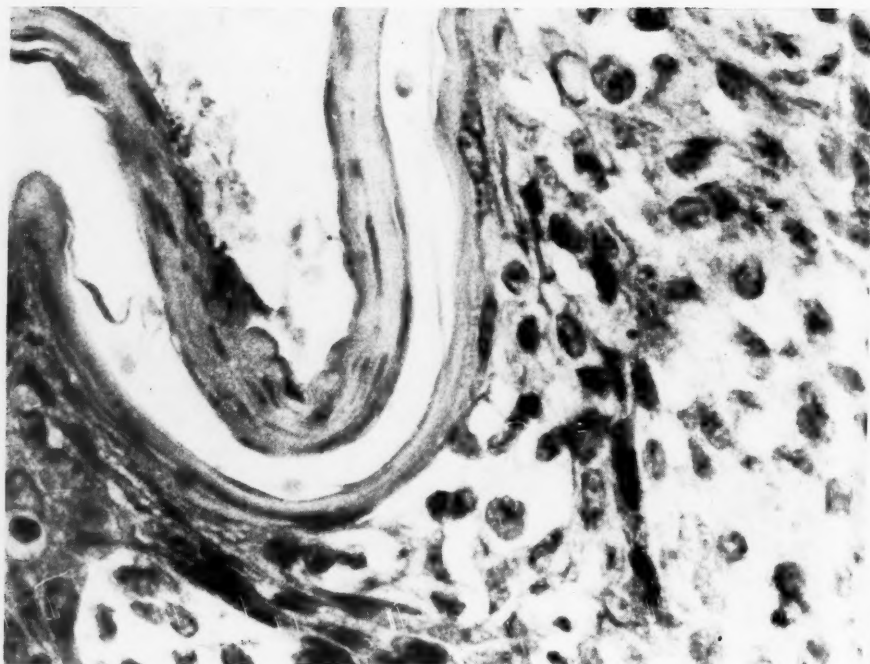


Fig. 2. (Detail of Fig. 1.) Shows a large number of histiocytes partly within the epidermis.

dition became worse and a significant progress of the skull defects was seen as bulging "tumours"; when the therapy was reinstituted the "tumours" decreased in size. The mechanism for the therapeutic effect of steroids is quite complicated and still unclear. It has been shown experimentally (8, 9, 17) that cortisone has a depressive effect on the phagocytosis and regenerative power of the reticuloendothelial system. The therapeutic effect of the corticosteroids can possibly be explained as such in non-lipid histiocytosis, on the supposition that this disease is caused by hyperactivity of the reticuloendothelial cells. It is well known that these cells especially phagocytize colloidal particles.

Thus, it has been suggested to use a colloidal radioactive substance which may destroy the proliferating histiocytes. Tristan et al. (22) reports a case of Letterer-Siwe's disease treated unsuccessfully with radioactive gold. This treatment has been used with some success in diseases affecting the lymphocytic elements (5). In two reported cases the intravenously administered colloidal gold Au^{198} has been localized by whole-body scintigram. No difference could be detected between the affected and unaffected skeletal parts. Nor did the scintigram show any accumulation in the "periphery", which would indicate increased absorption in the affected skin. As was expected, the uptake seemed most

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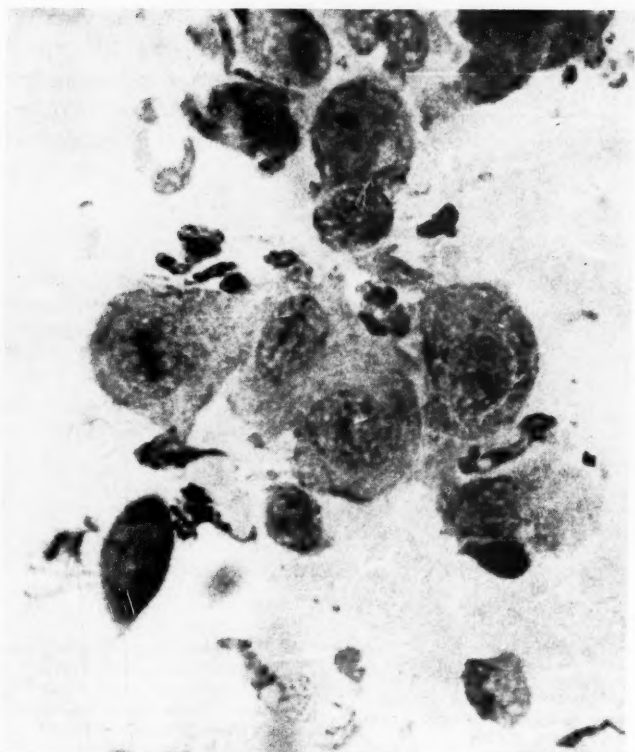


Fig. 3. Skin smear from a macula of "seborrheic eczema". Wright's stain. Small clusters of easily identified histiocytes having fine granular cytoplasm. (Yellow-orange filter. $\times 600$.)

marked in the liver and the spleen. The dosage of radioactive gold required to extend to the "periphery" has been calculated to be too toxic for therapeutic use.

The treatment of non-lipid histiocytosis is mostly palliative. Still it should not be discouraged in view of the bad prognosis of severely sick children. Cases have been reported (13) of definitely cured non-lipid histiocytosis, even of the most acute forms. Hence intense maintenance therapy with available means would seem justifiable also in severe cases.

Summary

The name non-lipid histiocytosis is introduced and defined to include eosinophilic granuloma, Hand-Schüller-Christian's disease and Letterer-Siwe's disease. Six cases are reported with particular emphasis on the early symptoms of refractory eczema in the capillitium and the auditory canals. The monocytosis in the peripheral blood and the gammaglobulin level are discussed. The value of skin smear as a diagnostic aid and the possibility of using it as screening test in refractory eczema

TABLE 1. *Six cases of non-lipid histiocytosis from KLB 1953-58.*

Cases . . .	1	2	3	4	5	6
Onset of symptoms (age in months)	3	5	5	9	12	12
Diabetes insipidus	-	+	-	-	-	+
Findings at X-ray of						
(a) skeleton	+	+	+	-	+	-
(b) lung	-	-	+	+	+	-
Cholesterol (mg/100 ml)	220	180	155	137	298	200
Monocytosis, %	3	5	22	14	11	5
Serumprotein, %	6.6	-	8.0	6.3	7.3	7.4
Relative % gammaglobulin	13.3	-	8.5	23.0	15.0	9.8
Age at present	29	56	(26) ^a	(13)	(34)	63

^a Figures in brackets indicate the age at death.

Histiocytose non lipoidique.

L'auteur décrit une série de 6 cas de granulomateuse réticulo-endothéliale généralisée en mettant spécialement l'accent sur les symptômes précoces d'eczéma rebelle du cuir chevelu et des tubes auditifs. Il traite de la monocytose dans le sang périphérique et du taux des gammaglobulines. Il examine la valeur des frottis cutanés en tant qu'auxiliaire du diagnostic et la possibilité de les utiliser comme épreuve de discrimination dans les cas d'eczéma rebelle. La valeur thérapeutique des stéroïdes et de la radiothérapie est mise en lumière. Dans deux cas, la résorption de l'or radioactif colloïdal a été étudiée à l'aide de scintogrammes couvrant tout l'organisme. La conclusion qui s'en dégage est que la dose curative requise est trop toxique pour qu'on puisse l'utiliser à des fins thérapeutiques.

Nicht-lipide Histiocytose.

Bericht über 6 Fälle von verallgemeinertem retikuloendotheliale Granulom mit besonderer Betonung der Frühsymptome in der Form eines widerspenstigen Ekzems des Kapillitiums und der Gehörgänge. Die Monozytose im peripheren Blut und der Gammaglobulinspiegel werden erörtert. Der Wert eines Hautabstrichpräparates

are considered. The therapeutic value of steroids and irradiation are illustrated. In two cases the uptake of colloidal radioactive gold was studied by whole-body scintigrams. It is concluded that the required curative dosage is too toxic for therapeutic use.

My thanks are due to Dr. B. Törnberg of the Pathology Department in the Karolinska Institutet, Sabbatsbergs Sjukhus, Stockholm, for his examination of biopsy material and skin smears, as well as of the autopsy material in Cases 3 and 5. Dr. B. Söderling of the Central Hospital in Borås, Sweden, has kindly placed data concerning Case 2 at my disposal.

als diagnostisches Hilfsmittel und die Möglichkeit seiner Verwendung als Rastertest bei widerpenstigem Ekzem werden erwogen. Der therapeutische Wert von Steroiden und Bestrahlung wird illustriert. Bei zwei Fällen wurde die Absorption von kolloidalem radioaktivem Gold mit Hilfe von Ganzkörper Scintogrammen studiert. Es wird geschlossen, dass die erforderliche Heildosis für therapeutische Zwecke zu toxisch sei.

Histiocitosis no lipodeica.

Presentación de seis casos de granuloma reticuloendotelial generalizado haciendo hincapié en los síntomas precoces de eczema refractario en el capilitium y conductos auditivos. Se discuten la monocitosis en sangre periférica y la cifra de gamma globulinas. Se consideran la utilidad del frotis cutáneo en el diagnóstico y la posibilidad de utilizarlo como screening test en el eczema refractario. Se ilustra el valor terapéutico de los esteroides y la irradiación. En dos casos se estudió el comportamiento del oro coloidal radioactivo mediante escintilogramas. Se concluye que la dosis curativa necesaria es demasiado tóxica para que pueda ser utilizada en la terapéutica.

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Pediatric Clinic
Polhemsgatan
Stockholm K
Sweden

From the Institute of Hygiene and Bacteriology, Department of Virology, University of Uppsala, Sweden.

A Small-Scale Trial of Attenuated Poliomyelitis Vaccine

by TORE WESSLÉN and HANS EKELEND

In 1958 only a few cases of poliomyelitis appeared in Sweden. During the interepidemic period from January until June no cases at all were reported in the County of Uppsala. In this free interval a vaccination with live poliomyelitis virus Type 1 was performed in this district in an institution caring for mentally retarded children. None of the children or the staff had been vaccinated before with inactivated poliomyelitis vaccine.

The vaccine selected for use was the triple plaque purified variant of the LSc-Sabin-strain (13).¹

The main purpose of the trial was to study the dissemination of the given virus in a population of individuals living close together and to obtain some information concerning the stability of the attenuated strain during passages in human beings. Virus excretion and antibody formation were also studied.

Population included in the trial

Thirty-seven children lived in the home where the test was carried out. They had diagnoses such as mongolism, birth-trauma and idiocy (without further diagnosis) and were fairly equally distributed in age groups from two to sixteen years except for one girl twenty years of age.

The staff including kitchen personnel consisted of nineteen persons and lived in a neighbouring house.

The younger children played together during the day in one dayroom and the older ones in another. They had some contact with each other and had shared bath and wash rooms. Four to eight children shared one sleeping room.

The kitchen was the same for the children and the staff and both had their meals in the home.

The hygienic standard of the institution could be regarded as very good.

During the week before the vaccination blood, throat and faeces specimens were taken from the whole population and assayed for the presence of viruses and neutralizing antibodies to poliomyelitis.

Only two of the children (called index children), both aged five years, were vaccinated. They received each 10,000 TCID₅₀ of the LSc-Sabin-strain in a glass of juice. Faeces specimens were then collected from both of them every day during the first week and then two times a week. Once a week faeces specimens were obtained from the other children and the staff. All children were followed in this way until at least three consecutive negative specimens had been obtained. Negative persons were followed until three consecutive negative specimens had been obtained from the last positive child.

During the first week the index children were also followed with daily throat swabs

¹ The authors are indebted to Dr A. Sabin for kindly supplying this vaccine.

and blood specimens for assay of poliomyelitis virus in throat and blood.

At the end of the trial which lasted fifteen weeks a second blood specimen was drawn from all of the children and the staff for assay of neutralizing antibodies to all three types of poliomyelitis virus.

Methods

Tissue cultures of trypsinized monkey kidney containing 1 ml of bovine amniotic fluid (BAF) with a 100 Units per ml of penicillin-streptomycin were used throughout.

From the faeces, ten percent suspensions were made in BAF containing 1000 Units per ml of penicillin-streptomycin. The suspensions were stored at -25°C and then tested in cultures for the presence of cytopathogenic virus. Three tubes which received 0.1 ml each were used per sample. Positive specimens were titrated by inoculation of serial tenfold dilutions of faeces suspensions into groups of 5 tubes. The virus recovered from the first culture passage was titrated in the same way and also typed against a Type 1 hyper-immune serum to assure that poliomyelitis virus Type 1 had indeed been recovered.

Some of the first culture passages were also chosen for intracerebral inoculations into monkeys and plaque efficiency tests. Both tests were performed as described before (19). Each specimen was tested in 4 rhesus monkeys and each monkey received one injection of 1 million TCD 50 in 0.5 ml. The observation period was one month.

Plaque tests were performed in flasks according to Melnick (7) with acid flasks containing 0.11 g% sodium bicarbonate and alkaline flasks containing 0.40 g% bicarbonate. One flask of each was used for each specimen tested. The inoculated amount was 100 TCD 50 per flask. A wild Type 1 strain and the LSc-Sabin-vaccine were always included as controls.

Neutralization tests were carried out as described before (19). Blood specimens from the beginning and the end of the trial were

tested undiluted against 100 ID₅₀ of all three types of poliomyelitis virus.

Throat swabs were extracted with 1 ml of BAF containing 1000 units per ml of penicillin-streptomycin. Point two ml of the resulting extract was inoculated into each of three culture tubes for virus assay.

Isolation of virus in blood was performed by inoculating 0.2 ml of blood into each of three culture tubes.

Results

The virus isolations from the throat and faeces samples obtained from the children and staff the week before vaccinations were all negative. No cytopathogenic virus other than poliomyelitis virus Type 1 was found in the population during the period of trial.

The prevaccination sera were tested for the presence of neutralizing antibodies to all three types of poliomyelitis. The results are given in Table 1. The immunogenic state of the population was found to be very favourable for a vaccine test with a Type 1 virus. Twenty-three (or 62%) of the children were triple-negative and as many as 84% had no antibodies to Type 1. The staff had a high degree of immunity. Only two of them lacked antibody to Type 1: one triple-negative, and the other one, the manager, had antibodies only to Type 2 and 3.

Clinical

After the LSc-Sabin-strain had been given, both index children and their contacts were thoroughly observed during the period of trial. No symptoms which could be related to the administration of poliomyelitis virus were detected. No paralysis appeared and no symptoms of non-paralytic poliomyelitis such as fever, stiffness of

TABLE 1. *Immunogenic state of population included in the trial before feeding of the LSc-sabin-strain.*

	<i>Number of subjects with antibodies for indicated types</i>						<i>Neg.</i>
	<i>I</i>	<i>II</i>	<i>III</i>	<i>I+II</i>	<i>I+III</i>	<i>II+III</i>	
Children	2	3	4	2	1	1	23
Staff	3	0	0	3	5	1	1
Total	5	3	4	5	6	2	24

the neck, etc., were observed. This was true also for the staff where no symptoms of minor illness were found. Neither were any gastrointestinal disturbances reported.

Excretion and dissemination of virus

Index children. Both children who were fed the LSc-Sabin-strain excreted Type 1 virus. The results from the examinations of throat and faeces specimens are given in Figs. 1 and 2. No viremia was detected. The duration of virus excretion with faeces was about five weeks for both children but the amount of excreted virus was much higher in one of them who had titres of 1 million TCD₅₀ per g of stools.

Contacts. There was a rapid spread of virus from the index children to the contacts and further. A week after the virus feeding two more children excreted virus in their faeces and one week later another thirteen children were positive. Altogether thirty-three subjects were found to excrete virus at one or several occasions. They are recorded in Figs. 1 and 2. Among the children, altogether thirty-two of thirty-seven excreted poliomyelitis virus Type 1 and one additional had changed from negative to positive against Type 1 in blood, without any cytopathogenic virus having been recovered from its faeces. Thus 90% of the contacts among the

children had positive evidence of infection with poliomyelitis Type 1 virus during the trial.

Among the staff the picture was quite different. No cytopathogenic virus was recovered on any occasion during the fifteen weeks of trial from any one of the seventeen subjects with "natural immunity" to poliomyelitis Type 1. Neither was there any evidence of infection of the manager who had negative faeces throughout and lacked neutralizing antibodies to poliomyelitis Type 1 before as well as after the trial. The remaining member of the staff, a fifty-year-old nurse who was triple negative in serum was infected two to three weeks after the vaccination and subsequently excreted virus for about a month.

The duration of virus excretion as well as the amount of excreted virus varied considerably among the contacts. In six of them only single positive specimens were found, five of which contained only small amounts of virus. Three of these individuals and another child with only two positive stools had neutralizing antibodies against poliomyelitis Type 1 virus in their prevaccination sera. Thus an infection with excretion of virus was detected in four of the 6 previously Type 1-immune children. They differed from the majority of non-

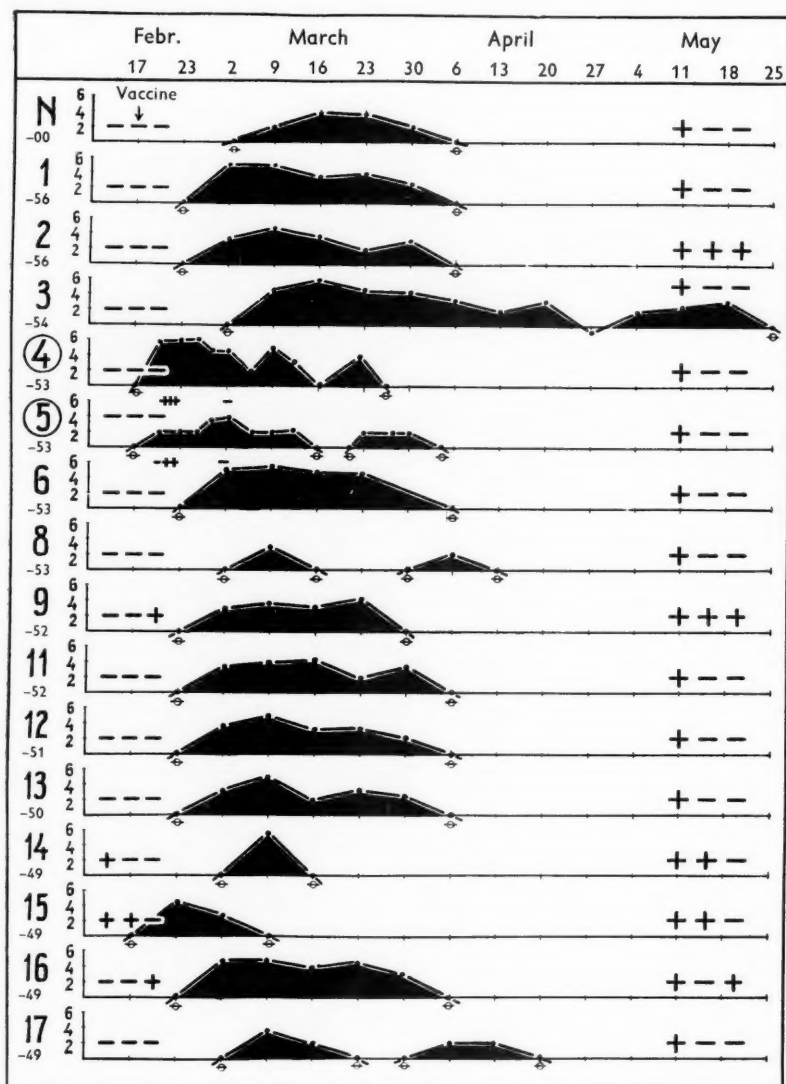


Fig. 1. Excretion of virus, TCD50 per g of faeces, in the two vaccinees, number 4 and 5 and the contacts found to have poliomyelitis virus in the stool. N is a nurse; the children are numbered according to age. Below the index children, presence or absence of virus in the throat is indicated. The sero-immune pattern against poliomyelitis Type 1, 2 and 3 at the beginning and the end of the trial is also indicated.

⊖ indicates negative stool.

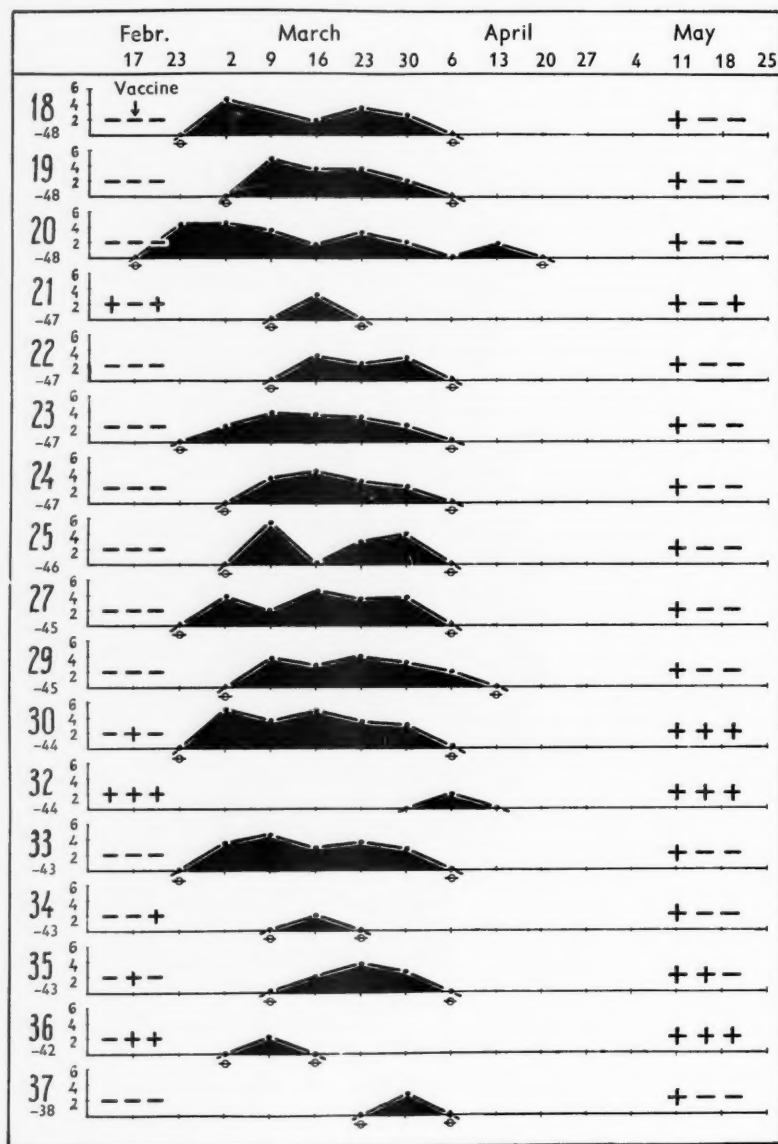


Fig. 2. Continuation of Fig. 1.

immunes by the small and short excretion of virus. On the other hand, a short excretion of small amounts of virus was also observed in three subjects without any demonstrable neutralizing antibodies to Type 1, one triple negative, one with antibodies to Type 2 and one with antibodies to Type 2 and 3. These individuals might have had small amounts of antibodies beyond the level which can be detected in tests against 100 TCD₅₀ of virus. Repeated tests against 100 TCD₅₀ were, however, still negative.

In contrast to these short-excretors, one triple sero-negative child four years of age, yielded large amounts of virus in her faeces during a period of three months.

Antibody responses

All subjects lacking Type 1 antibodies at the beginning of the trial and from whom virus was isolated were found to have produced neutralizing antibodies to poliomyelitis Type 1 at the end of the observation period. One of the children had changed to sero-positive although no virus had been recovered from its faeces. It might have had a short excretion of virus which was not detected.

Two children and one adult remained negative against Type 1.

Besides these antibody responses to the homologous virus there were some heterologous responses among the virus positives. Two children without detectable neutralizing antibodies to Type 2 and one without Type 3 antibodies had acquired antibodies to Type 2 and 3 respectively, after the Type 1 infection. None of the other subjects negative to Type 2 or 3 had changed and there was no evidence of any Type 2 or 3 infections in the population

during the period of trial. Heterologous antibody responses of the same sort have been found before in connection with vaccination with formalinized poliomyelitis virus and it seems reasonable to assume an anamnestic response also in the present cases. They might have had antibody levels below that detectable with the method used.

Virulence of the excreted virus

In order to study the stability of the LSc-Sabin-strain during passages in the human gut the virus excreted by the vaccinees and their contacts was investigated for plaque-characteristics and intracerebral activity in rhesus monkeys.

Plaque tests. Vogt *et al* (18) found that attenuated strains of poliomyelitis virus did not give plaques in cultures with an agar-overlay of low bicarbonate concentration (d variants), in contrast to wild paralytogenic strains which gave plaques of about the same size in these cultures as in cultures with a high content of bicarbonate (d + variants). As was shown later by Sabin (12) and others (7) the plaque characteristics of a strain of poliomyelitis virus do not give a true picture of its attenuation. Strains have been found which have changed from d variants to d + variants although no increase in their neuropathogenicity could be demonstrated (7). Although changes of the d characteristics of the LSc-Sabin-strain in d + direction consequently can not be regarded as an indication of increased neurotropism it is one way to find a change in the original characteristics of the vaccine strain in studies of its stability. A rough estimation of the plaque-characteristics of the excreted virus from the twelve subjects

TABLE 2. *Plaque characteristics of the excreted virus from the twelve first subjects.*

Subject No.	Virus-Containing Faeces No.									
	1	2	3	4	5	6	7	8	9	10
N	—	—	—	—						
1	—	—	+	+	—					
2	+	+	+	+	+					
3	—	—	+	+	+	+	+	+	—	—
4	—	—	—	—	+	+	+	—	—	—
5	—	—	+	+	+	+	+	+	—	—
6	+	+	+	+	+					
8	+									
9	—	—	—	—						
11	—	—	+	—	—					
12	—	+	+	—	—					
13	—	+	+	+	+					

For further information see Fig. 1 and text.

first listed in Fig. 1 was therefore made. About 100 TCD₅₀ was inoculated in flasks of high and low bicarbonate content. In our hands the results of one testing were, however, difficult to reproduce in another. The ratio between the number of plaques in each type of culture as well as the time of appearance of plaques differed in batches from different kidneys. In some batches small plaques appeared in the acid cultures while the same specimens tested in other batches were negative. The virus recovered from some of the stools seemed, however, to give more clear results with larger and more distinct plaques in the flasks of low bicarbonate content. In these cases the plaques in corresponding flasks of high bicarbonate content were rapidly growing, large plaques. These specimens were regarded as containing d+ variants and are indicated by a plus in Table 1. Many factors may influence the plaque characteristics (6). The results indicate, however, that a change in d+ direction occurred in most children tested but not in the adult, and that the d+ particles did not overgrow the other but

rather that the d particles usually were dominating at the end of the excretion period. Two children had d+ excretions throughout. The virus recovered from one of them appeared to be the most paralytogenic of those used for inoculation of the monkeys.

Monkeys tests. Specimens from ten different subjects were tested intracerebrally in rhesus monkeys. The culture fluid from the first tissue culture passage of the excreted virus was diluted to give 1 million TCD₅₀ in 0.5 ml which was given in one injection.

Four monkeys inoculated with 0.5 ml of the undiluted vaccine remained healthy during the whole observation period. No virus could be isolated from their CNS and no poliomyelitic lesions were found on microscopic examination.

Culture fluids from one of the first stools containing large amounts of virus were then chosen as virus source for the monkey tests. Some of the monkeys inoculated with the virus recovered from the stools came down with paralysis. Altogether en

TABLE 3. *Results of intracerebral testing of the first culture passage of poliomyelitis virus excreted by the vaccinees and their contacts. Each monkey obtained one million TCD50 in 0.5 ml.*

Subject	Date of faeces collection	Days after first positive specimen	Paral	Incubation time, days	Virus in CNS
N	16/3	7	0/4		0/4
1	9/3	7	2/4	21, 22	1/4
1	30/3	28	0/4		0/4
2	9/3	7	0/4		0/4
3	6/3	7	2/4	11, 21	2/4
3	18/3	70	0/4		0/4
4	23/2	3	0/4		0/4
5	2/3	8	1/4	15	1/4
6	16/3	14	3/4	12, 14, 17	2/4
6*	16/3	14	1/3	7	0/3
6	30/3	28	0/3		0/3
8	9/3	0	1/4	17	0/4
33	9/3	7	0/4		0/4
35	23/3	8	0/3		0/3

* Only 10,000 TCD50 inoculated

of fifty-three monkeys were paralyzed and some additional monkeys had histological evidence of a poliomyelitis infection in the brain and spinal cord. The results are given in detail in Table 3. Half of the subjects tested were found to excrete a virus with intracerebral activity in monkeys. In one case three of four monkeys were paralyzed and in two other cases, two of four monkeys. Virus from the first case was found to give paralysis in one of three monkeys also when only 10,000 TCD50 had been inoculated. Sabin (7, 13) has reported that the excretion of a more neurotropic virus which could sometimes be detected seems to be only temporary and does not continue during the whole period of virus excretion. From the above three children the last stools found to contain virus were therefore also tested in monkeys. No paralyzes were observed in any of the monkeys inoculated with virus

from these stools. The results thus indicate that also in the present cases the excretion of a more neurotropic virus was only temporary.

The severity of the paralysis in the monkeys varied considerably as well as the incubation time before onset of paralysis. Some cases had severe paralysis and were moribund when they were killed; others had severe or mild paralysis of one or both legs. Besides the ten paralytic monkeys there were some additional animals with a suspicious weakness in the hindlegs but which were not classified as having paresis because the clinical picture was not quite clear. They were among those found to have poliomyelitic lesions in the CNS. The average time before the onset of the paralysis was longer than after inoculation of most wild strains.

Poliomyelitis virus could not be recovered from the CNS of all paralyzed mon-

keys. In five cases virus was found in both the spinal cord and the brain and in one additional case only in the spinal cord. No virus was recovered from the four remaining monkeys with paralysis. No further attempts were made to isolate virus from these monkey cords by using more diluted suspensions or by passaging the negative tubes in the first culture passage. As reported earlier by Sabin (11, 14) it has been repeatedly found in studies of attenuated strains that no virus can be recovered from the CNS of some of the paralytic monkeys due to the fact that strict neurotropic, noncytopathic mutants may arise during the course of viral multiplication in the brain. These findings together with the fact that only a limited number of monkeys were used makes it difficult to draw any certain conclusions about the degree of increase of neuro-pathogenicity or the amount of paralytogenic particles present in the stools. The histological examinations show an involvement of the spinal cord of a great deal more monkeys than those paralyzed. It is thus evident that the virus proliferation in at least one half of the individuals tested was associated with an increase in the neurotropic activity.

All viruses isolated from the CNS of the paralyzed monkeys were Type 1. Only the above reported viruses were used in the unit housing the monkeys during the period under which the tests were carried out.

Discussion

As has been pointed out before, the best way of achieving a sound assessment of live poliomyelitis vaccines seems to be by an increasing amount of carefully performed small scale studies in many places

followed by large scale trials if the accumulated evidence from the small scale trials allow a further step. American workers (8, 13, 14) have pioneered in this field and the attenuated strains developed by them are now tested by a number of virologists in different parts of the world. The present investigation is one of the small scale contributions. We have studied what happens when the LSc-Sabin-strain of poliomyelitis virus Type 1 is introduced in an institution with mentally retarded children and their nurses. As the most important question is the reaction of a normal population with a low immunity upon a vaccination with live poliomyelitis virus, normal untreated families would be the most preferable population to be chosen for a vaccination trial. Certain risks must however be taken in a vaccination of such a non-isolated population because there is not yet enough evidence to show that the disseminated virus excreted from the vaccinees may not be paralytogenic. Investigations similar to the one reported here have shown an increased paralytogenic activity in monkeys of the excreted virus. In vaccination experiments performed with volunteers Sabin (13, 14) found only a low increase and so did Horstmann *et al* (4, 5) and Verlinde (17) in vaccinations with Sabin's strains. Clarke *et al* (1) using the same Type 3 strain reported, however, a much higher increase of neurotropic activity in intracerebrally injected monkeys of the virus which had propagated in the alimentary tract. They isolated from one of the vaccinees a virus which they found to have regained its power to paralyze monkeys to the same extent as do field strains of Type 3 virus from paralytic cases.

Also in vaccination experiments with the attenuated strains selected by Koprowski different results are reported concerning the stability of the virus after propagation in the human gut. Koprowski himself (10) did not observe any increase in paralytogenic activity of the excreted virus and da Silva (15) found only very slight increase while Dane & Dick (2) found an increase of paralytogenic activity to such an extent that they regarded the TN and SM strains unsuitable as a vaccine on grounds of safety. In a previous work (19) with some of Sabin's attenuated strains we had some evidence that the propagation of attenuated strains in human cells can bring about a more paralytogenic virus population also when the virus propagation takes place in cells kept in tissue cultures in vitro.

Divergent results have also been reported concerning the ease with which different attenuated strains of poliomyelitis virus might spread from vaccinees to contacts and further (2, 4, 9, 14).

The population included in the present study lived under conditions analogous to those existing in family life but the fecal contamination was greater due to the fact that most individuals included were low grade mental defectives. A day nursery with small children might have a contamination of the same degree and might possibly be compared with the study population.

The spread of virus we found after feeding of the LSc-Sabin-strain to only two of the children is very much the same as previously found in studies of poliomyelitis epidemics in day nurseries or similar institutions (3, 16). Ninety per cent of the contacts among the children had positive

evidence of infection, which is in good agreement with the ninety two per cent infected associates found by Horstmann *et al* (4) in a group of "vaccine immune" children in a similar vaccination trial with the LSc-Sabin-strain. We also found the same short incubation period as they did. The first virus positive contacts appeared already a week after the virus feeding. New infected individuals were then detected over a long period, making it more probable that the infection was transmitted by contact and not by any source in common which could have given a heavy dose of virus on one occasion. The results thus indicate that the ease with which the LSc-Sabin-strain spread to close associates is the same as for wild strains of poliomyelitis virus.

Of considerable interest is also the fact that four of the Type 1 sero-positive children excreted virus while on no occasion during the whole trial was any virus excretion observed among the eighteen members of the staff possessing Type 1 antibodies. The only virus-positive adult lacked antibodies to all three types. These observations confirm earlier findings that it is possible to reinfect some "naturally immune" individuals, and support earlier assumptions that the age and probably the number of previous poliomyelitis infections is an important factor for the resistance of the alimentary tract to new infections (4).

The short excretion of small amounts of virus found in the children with homotypic antibodies was also observed in three individuals in whom no homotypic antibodies could be detected. Other factors than a high titre of homotypic antibodies may therefore be of importance for the

duration and strength of the poliomyelitis infection in the alimentary tract (14).

To obtain a true picture of the neurotropism of all viruses recovered from the two vaccinated individuals and their virus positive contacts requires a very large number of monkeys. The limited number at our disposal seems, however, to have given some information. The fact that nine out of fifty monkeys were paralyzed after intracerebral inoculations of 1 million TCD50 of viruses from the stools shows that neurotropic mutants may arise during the course of viral multiplication in the human gut. This is in agreement with the results reported by most investigators who have studied the virus excreted by individuals vaccinated with different live, attenuated strains of poliomyelitis virus (1, 2, 14). The virus recovered from one child gave paralysis in three of four monkeys given 1 million TCD50 and one of three monkeys inoculated with 10,000 TCD50, which indicates that in some individuals infected with the LSc-Sabin-strain, the virus multiplication may be associated with a considerable increase in the paralytogenic activity for monkeys. The viruses recovered from two other small children both paralyzed two of four monkeys. The last stools found to contain virus from these three children were also tested in monkeys in the same way but were found to cause no paralysis. Sabin (7, 13) and Verlinde (17) have earlier reported similar findings indicating that the human alimentary tract does not preferably select poliovirus particles of greater neurotropism. The excretions of more neurotropic virus has been found to be only temporary, probably due to overgrowth by a majority of non-paralytogenic particles. Our results

from the plaque efficiency tests of the excreted virus indicate that also the appearance of d+ variants in most individuals is only temporary. Although all available evidence points to a dominating role of particles like the original virus, it is evident that paralytogenic particles may appear at least for some time in some persons depending upon unknown factors. It is also evident that an attenuated strain probably may have the same high contagiousity as a wild paralytogenic strain. Consequently there is a great chance that also the paralytogenic particles excreted to a certain extent will be transmitted to contacts. This offers special problems not previously encountered with other vaccines employed in human beings.

In a mass vaccination with an attenuated strain of poliomyelitis virus there will always be a large number of people not willing to be vaccinated but who cannot escape an infection from the vaccines. The overgrowing of the nonparalytogenic particles makes it probable that the dominating virus in the population would be of the attenuated type, but the most important problem seems to be what would happen if someone became infected with only paralytogenic particles. Would this start a "sideline" of paralytogenic virus which might give rise to an epidemic in a neighbouring or other district? It seems reasonable to assume that this is exactly what happens in nature when a more pathogenic mutant of a generally relatively nonvirulent virus is appearing somewhere and then starts an epidemic.

It is, however, difficult to draw any conclusions about the paralytogenicity for man of the excreted virus from the available data concerning the increase in

"cerebral activity" for rhesus monkeys. Even the most neurotropic excretions found may still contain a virus which when introduced orally in human beings would give no paralysis. All vaccination experiments with attenuated poliomyelitis viruses reported hitherto as well as our own have been performed without any untoward reactions having been observed in the vaccinees or their contacts. Only carefully followed-up, large-scale vaccinations will give full information concerning the importance of the virus of increased neurotropism which undoubtedly may appear in the stools of individuals vaccinated with attenuated strains of poliomyelitis virus.

Summary

A vaccination experiment with the LSc-Sabin-strain of attenuated poliomyelitis virus Type 1 was performed in an institution for mentally retarded children during an interval free from poliomyelitis. Thirty-seven children and the staff, nineteen persons, were included in the trial. Before administering the virus, sixty-two per cent of the children were triple sero-negative and eighty-four per cent negative to Type 1. Among the staff only two persons lacked neutralizing antibodies to Type 1.

Only two of the children were fed virus. Both excreted virus and a rapid dissemination occurred, infecting ninety per cent of the children and one of the two Type 1 negative nurses. Four of six children with naturally acquired Type 1 antibodies became infected and had virus in their stools in contrast to Type 1-immune adults who had no evidence of infection.

Virus excretion in the stools was of

short duration in the four immune children, but varied considerably in those without any demonstrable antibodies—from single positive stools to three months of virus excretions. There were also great variations in the amounts of excreted virus. Titres up to one million TCD₅₀ per g of faeces were recorded.

None of the infected subjects showed any evidence of illness attributable to virus infection. All of the Type 1-negative subjects found to excrete virus during the trial had changed to Type 1-positives by the end of the trial, suggesting a one hundred per cent immunizing effect of the LSc-Sabin-strain.

Virus in the first tissue culture passage recovered from the stools of ten different subjects was tested intracerebrally in rhesus monkeys. Half of the subjects tested were found to excrete viruses inducing paralysis after inoculation of one million TCD₅₀. Altogether ten of fifty-three monkeys were paralyzed. However, virus could only be recovered from six of them, indicating that in the other four the paralysis was due to a neurotropic, non-cytopathogenic variant selected in the course of virus multiplication in the CNS of the monkey.

In three children possessing "monkey positive" excretions at the beginning of the excretion period, virus from the last positive stools did not induce any paralysis, suggesting an overgrowth by the nonparalytogenic particles during the course of virus multiplication in the human gut.

It is pointed out that the evidence so far indicates that most attenuated strains of poliomyelitis virus tested in human beings may easily spread to close contacts

and a more paralytogenic mutant may temporarily appear in the stools of some individuals. The most important problem in connexion with mass vaccination with live, attenuated strains therefore seems to be what happens in persons infected with

a majority of paralytogenic particles. There seems to be a certain risk that "sidelines" of more neurotropic viruses may be started although the dominating virus in a vaccinated population will be of the attenuated type.

Essai à échelle réduite, du vaccin anti-poliomyélique à virus vivant atténué.

Une expérience de vaccination à l'aide de la souche LSc de Sabin, composée de virus poliomyélique atténué du Type 1, a été réalisée dans une communauté d'enfants psychiquement retardés; le personnel soignant (19 personnes) a été également compris dans l'expérience. Avant la vaccination, 62 % des enfants ne présentaient aucun anti-corps vis-à-vis des trois Types de virus et 84 %, vis-à-vis du Type 1. Deux membres du personnel, ne possédaient pas d'anti-corps contre le Type 1. Deux enfants seulement ont absorbé le virus atténué; tout deux excrétèrent du virus et la dissémination du virus dans la communauté fut rapide : 99 % des enfants et une des deux infirmières qui ne possédaient pas d'anti-corps contre le Type 1, ont été infectés. Parmi les six enfants qui possédaient déjà des anti-corps contre le type 1, quatre furent infectés : on a retrouvé du virus dans leurs selles. Par contre, chez les adultes possédant déjà des anti-corps contre le Type 1, aucun signe d'infection n'a été mis en évidence. L'excrétion de virus dans les selles a été de courte durée chez les quatre enfants naturellement immuns. Chez les enfants dépourvus d'anti-corps naturels, la durée d'excrétion du virus variait considérablement. Chez certains, le virus n'a été retrouvé que dans une seule selle; chez d'autres, l'excrétion du virus s'est prolongée pendant trois mois. La quantité de virus excrété variait également dans de larges proportions : des concentrations atteignant un million de TCD 50 par gramme de matière fécale ont été détectées. Les sujets infectés n'ont présenté aucun signe pathologique qui puisse être attribué à l'infection virale. Tous les sujets qui ne possédaient pas d'anti-corps et qui ont excrété du virus pendant l'expérience, avaient acquis des anti-corps vis-à-vis du Type 1, à la fin de l'expérience : ceci incite à penser que la souche LSc de Sabin peut atteindre un taux d'efficacité de 100 %. Les virus trouvés dans les selles et pris après leur premier passage sur culture de tissus, chez 10 sujets différents, ont été injectés dans le cerveau de singe rhésus. La moitié de ces sujets

excrétait des virus capables de provoquer l'apparition de paralysie à la suite de l'inoculation d'un million de TCD 50. Au total 10 singes sur 53 ont présenté des paralysies. Cependant le virus n'a été retrouvé que chez 6 singes; chez les 4 autres singes les paralysies ont été provoquées par un variant neurotrophique, mais non cytopathogénique, sélectionné au cours de la multiplication du virus dans le système nerveux cérébro-spinal du singe. Chez trois enfants dont les selles présentaient du virus « positif pour le singe » au début de la période d'excrétion du virus, le virus de la dernière selle positive n'a pas provoqué de paralysie : il semble que les virus non paralytogenes se soient développés d'une manière excessive et préférentielle au cours de la multiplication du virus dans l'intestin humain.

Versuch in kleinerem Maassstab mit antipoliomyelitischen Vaccin von lebenden, abgeschwächten Viren.

Ein Vaccinationsversuch mit Hilfe des Stammes LSc von Sabin, der aus abgeschwächtem Poliomyelitisvirus vom Typ 1 bestand, wurde an einer Gruppe von psychisch zurückgebliebenen Kindern durchgeführt, das Pflegepersonal (19 Personen) wurde auch zu den Versuchen herangezogen.

Vor der Vaccination zeigten 62 % der Kinder keine Antikörper gegen die 3 Virustypen und 84 % hatten keine Antikörper gegenüber Typ 1. Nur zwei Kinder haben das abgeschwächte Virus aufgenommen, alle beide schieden Virus aus, und die Verbreitung des Virus in der Gruppe erfolgte schnell. 99 % der Kinder und eine der beiden Krankenpflegerinnen, die keine Antikörper gegen den Typ 1 besaßen, wurden infiziert. Von den 6 Kindern, die schon Antikörper gegen den Typ 1 besaßen, wurden 4 infiziert, man fand das Virus in ihren Faeces. Dagegen wurde bei den Erwachsenen, die schon Antikörper gegen den Typ 1 besaßen, keine Zeichen der Infektion offenbar. Die Ausscheidung des Virus mit den Faeces war bei den natürlich immunen Kindern von kurzer Dauer.

Bei den Kindern ohne natürliche Antikörper variierte die Dauer der Ausscheidung des Virus beträchtlich. Bei einigen wurde das Virus nur in einem Stuhlgang gefunden, bei anderen hielt die Ausscheidung des Virus 3 Monate an. Die Menge des ausgeschiedenen Virus wechselte auch in weiten Grenzen, Konzentrationen bis zu einer Million von TCD 50 per Gramm fäkalen Materials wurden beobachtet. Die infizierten Fälle zeigten keinerlei pathologische Zeichen, die der Infektion mit dem Virus zugeschrieben werden könnten. Alle Fälle, die keine Antikörper besaßen, und die das Virus während der Versuche ausschieden, hatten am Ende des Experimentes Antikörper gegen den Typ 1 erworben: dieses läßt vermuten, dass der Stamm LSc von Sabin einen 100%igen Grad der Wirksamkeit erreichen kann. Die bei 10 verschiedenen Versuchspersonen in den Faeces gefundenen Viren wurden nach ihrer ersten Passage auf einer Gewebekultur entnommen und in das Grosshirn von Rhesusaffen injiziert. Die Hälfte der Versuchspersonen schied Viren aus, welche fähig waren, nach Inoculation von einer Million TCD 50 Lähmungen zu erzeugen. Insgesamt zeigten 10 von 53 Affen Lähmungen. Dagegen wurde aber das Virus nur bei 6 Affen wiedergefunden, bei den anderen 4 Affen waren die Lähmungen hervorgerufen von einer neurotopen, aber nicht Cytopathogenen Variante, die sich im Laufe der Vermehrung des Virus im cerebro-spinalen Nervensystem des Affen herausgebildet hatte. Bei drei Kindern, deren Faeces zu Beginn der Virusausscheidung „viruspositiv für den Affen“ waren, erzeugte das Virus der letzten positiven Faeces keine Lähmungen, es scheint, als ob die nicht Lähmungen hervorriefenden Viren sich durch eine übermässige und bevorzugte Weise im Verlauf der Vermehrung des Virus im menschlichen Darm entwickelt hätten.

Ensayo en pequena escala de vacunación anti-poliomielítica por virus atenuado.

En una institución para niños deficientes mentales, se realizó una experiencia de vacunación utilizando la cepa LSc-Sabin de virus

atenuados del Tipo 1. El personal de dicha institución, 19 personas, fué incluido en el ensayo. Antes de la administración del virus, el 62 por ciento de los niños eran triple seronegativos, y 84 por ciento, negativos al Tipo 1. Sólo 2 individuos entre el personal carecían de anticuerpos neutralizantes frente al Tipo 1. Solamente 2 de los niños ingirieron el virus. Ambos excretaron el virus, que se difundió rápidamente, infectando al 90 por ciento de los niños y a 2 de las enfermeras Tipo 1 negativas. Cuatro de 6 niños con anticuerpos Tipo 1 adquirido naturalmente, se infectaron y el virus fué aislado en sus heces, en oposición a los adultos Tipo 1 inmunes, en los que no hubo evidencia de infección. En los 4 niños inmunes la excreción del virus fué de corta duración, pero varió considerablemente en aquellos sin ningún anticuerpo demostrable: desde una sola deposición positiva, hasta tres meses de eliminación del virus. Fueron hallados títulos de hasta un millón TCD 50 por gr. de materias fecales. Ninguno de los individuos infectados mostró evidencia de enfermedad atribuible a infección virósica. Todos aquellos Tipo 1 negativos en que se halló excreción del virus durante el experimento, viraron a Tipo 1 positivos hacia el fin de la prueba, sugiriendo que la cepa LSc-Sabin es susceptible de conceder inmunidad en el cien por ciento de los casos. Se inoculó intracerebralmente, en el mono Rhesus, virus provenientes de las heces de 10 sujetos diferentes, tomados de su primer pasaje en cultivo de tejidos vivos. La mitad de entre ellos demostraron eliminar virus capaces de producir parálisis luego de la inoculación de un millón TCD 50. En total, 10 entre 53 monos exhibieron formas paralíticas. Sin embargo, el virus pudo ser recuperado en sólo 6 de ellos, indicando que la parálisis, en los 4 restantes, fué debida a una variante no citopatogénica, néutrónica, producida por selección en el curso de la multiplicación viral en el SNC del mono. En 3 niños que poseyeron excreción «mono positiva» al comienzo del período de excreción, los virus de las últimas deposiciones positivas no produjeron ningún tipo de parálisis, sugiriendo un crecimiento invasivo de partículas no paralitogénicas durante el curso de la multiplicación del virus en el intestino humano.

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Dept. of Virology
Institute of Hygiene and Bacteriology
Uppsala
Sweden

The 24-Hour True Endogenous Creatinine Clearance in Infants and Children without Renal Disease

by JAN WINBERG

Simultaneous estimation of "specific" endogenous creatinine clearance (C_{CR}) and inulin clearance (C_{IN}) gives a $C_{CR}:C_{IN}$ ratio so close to unity that it justifies using C_{CR} as a measurement of the glomerular filtration rate (GFR) in healthy subjects (3, 4, 14, 15, 16, 19). The constancy of the serum creatinine level and of the urinary excretion of endogenous creatinine makes it possible to determine C_{CR} during 24-hour periods (1, 7), which will give an estimation of the GFR under more physiological conditions than those obtained in short term experiments.

Since the 24-hour C_{CR} determination results in relatively little discomfort to infants and children and therefore is useful, especially when repeated examinations are desired, it was thought worthwhile to give an account of the present investigation, which was originally performed in evaluating renal function in infants and children with urinary tract infections.

Material and Methods

Material. The material consisted of 38 infants and children between the ages of 3 days and 14 years. They were patients with diseases judged to have no significant influence

upon renal function. The patients were all in good general condition and showed no evidence of renal or cardiovascular disease or anemia. Three patients over the age of 1.5 years had been in bed for about 2 weeks before the clearance determinations were performed. The other patients of the same age group had been confined to bed for less than one week. Only four girls were included in the material, all more than three years of age.

Procedure. The patients received an ordinary ward diet in which, however, meat was replaced by fish or eggs for two days preceding and during the urine collection periods, as suggested by Camara, Arn, Reimer & Newburgh (7). Urine was collected during two consecutive 24-hour periods, during which time the children were kept in bed. Blood samples were drawn in the morning under fasting conditions.

In small children urine was collected by means of a glass tube attached with adhesive tape to the baby restrained in a sloping bed. Rubber tubing from the glass tube delivered the urine to a collecting bottle without pooling. A weighed cotton pad placed under the glass tubing was observed carefully and weighed after any soiling. A loss to the pad of 10 per cent or less by weight was added to the total sample collected. The sum of these quantities was then multiplied by the urinary creatinine concentration to obtain the total creatinine excretion. If the loss was more than 10 per cent, the whole 24-hour sample was discarded.

Accurate 24-hour urine sampling in older children necessitates meticulous instruction to both ward staff and patient. The many pitfalls of prolonged collection are well outlined by de Wardener (24).

Calculation of the clearance. Clearance was calculated according to the usual formula $\frac{U \times V}{P}$, cf. Smith (22). When two plasma creatinine determinations were performed in the same patient the mean of these values was used.

All clearance values were corrected to a standard body surface area of 1.73 sq.m. The reliability of the estimation of the body surface area, especially in children, by means of the Du Bois height and weight formula can be doubted, but this standard of reference is now definitely accepted within the field of renal physiology. Support of the use of this principle in infants is given by Rubin, Bruck & Rapoport (20). It can be mentioned, however, that recently Friis-Hansen (12) has suggested that the volume of the extracellular fluid

TABLE 1 A. *Recovery of creatinine added to plasma.*

Original conc. of creatinine mg per 100 ml	Added creati- nine mg per 100 ml	Calculated conc. in mg per 100 ml	Observed conc. in mg per 100 ml
1.07	0.1	1.17	1.16
(1.07 - 1.07)	0.1	1.17	1.16
	0.2	1.27	1.27
	0.2	1.27	1.28
	0.3	1.37	1.38
	0.3	1.37	1.37
	0.4	1.47	1.48
	0.4	1.47	1.52
	0.5	1.57	1.55
	0.5	1.57	1.56

TABLE 1 B. *Recovery of creatinine added to urine.*

Original conc. of creatinine mg. per 100 ml	Added creati- nine mg per 100 ml	Calculated conc. in mg per 100 ml	Observed conc. in mg per 100 ml
0.35	0.1	0.45	0.47
(0.34 - 0.36)	0.1	0.45	0.47
	0.2	0.55	0.53
	0.2	0.55	0.54
	0.3	0.65	0.61
	0.3	0.65	0.61
	0.4	0.75	0.72
	0.4	0.75	0.72
	0.5	0.85	0.81
	0.5	0.85	0.81

would be a better standard of reference when glomerular filtration rate in infants and adults are compared.

The five patients below the age of 2 weeks occupy a particular position since in these cases there seemed to be a systematic decrease of the plasma creatinine concentration during the period of investigation (Table 3). The plasma creatinine values used in the calculation of the C_{CR} in these cases were obtained by extra- and interpolation of the estimated plasma values to the midpoint of the urine collection periods. The extra- and interpolation was performed under the assumption of a linear decrease of the plasma creatinine concentration.

Analytical Methods. Endogenous creatinine in plasma and urine was determined after absorption with Lloyd's reagent (Fuller's Earth B.D.H.) according to the method of Hare (13). With this technique only the true creatinine is measured. The method was adapted for colorimetry in a Beckman B spectrophotometer and performed in the following manner. Urine was initially diluted

TABLE 2. Statistical calculation of errors of creatinine analysis and of physiological variation of plasma creatinine concentration and creatinine clearance.¹

	Mean diff. (D) (n) ³	s.d. _D	Error of method ² absolute	%	Mean of deter- minations (range)
Error of analysis					
Plasma creatinine mg/100 ml	-0.0030 ± 0.6021 (81)	0.019	0.014	2.9	0.48 (0.21 - 1.13)
Urine creatinine mg/100 ml	-0.38 ± 0.20 (25)	0.98	0.69	1.7	40 (6 - 121)
Error arising from physiologic variation from day to day					
Plasma creatinine con- centration mg/100 ml (children ≤ 3 years)	+0.0013 ± 0.0090 (16)	0.036	0.025	5.8	0.44 (0.24 - 0.67)
C _{CR} ml/min./1.73 sq. m. (children < 3 years)	-0.45 ± 1.63 (20)	7.28	5.15	5.8	88 (62 - 149)
C _{CR} ml/min./1.73 sq. m. (children > 3 years)	-2.08 ± 3.08 (12)	10.7	7.5	6.7	113 (94 - 142)

¹ Error of method determined according to method of double determinations. 1st-2nd value = D.
s.d._D = standard deviation of differences. Error of method = s.d._D/√2.

² Standard deviation of one estimate.

³ n = number of cases.

with distilled water to a desired concentration of creatinine between 0.5 and 2.5 mg per 100 ml. One ml samples of plasma and diluted urine were used. The proportions of plasma and urine to the reagents were the same as proposed by Hare. Readings were made in 10 mm cuvettes at 500 mμ. The colour was stable for at least 55 minutes. All samples were read within this time. Duplicate determinations were regularly performed. When known amounts of creatinine were added to plasma and urine the recovery was found to be very good. (Table 1.)

In calculating the errors of analysis statistically, the method of double determinations, cf. Dahlberg (8), was used. The error of method (standard deviation of one estimate) was 0.014 mg/100 ml in the determination of plasma creatinine and 0.69 mg/100 ml in the determination of urine creatinine (Table 2). The differences between individual pairs of observation were also plot-

ted against the corresponding mean. No correlation between differences and mean could be observed, hence the absolute differences were used here. The errors in percentage may be calculated from the mean of all determinations (Table 2).

Results and Discussion

I. Accuracy of the technique

First, a few points elucidating the accuracy of the experimental conditions of this investigation will be discussed.

The reproducibility of the 24-hour C_{CR} determination was good. The total error in one 24-hour value, arising from the variation during two consecutive 24-hour periods (calculated according to the method of double determinations) was 5.8

TABLE 3. *True endogenous creatinine clearance in children without renal disease (24-hour urine collection periods).*

Case	Age in days	True endogenous C _{CR}		Plasma creatinine conc. mg per 100 ml	Diuresis ml/24 h.	Urine loss in per cent of diuresis
		lit./24 h./1.73 sq. m.	ml/min./1.73 sq. m.			
1	4	39	27	0.53	20	0
	5					
	6	53	37		22	0
	7	55	38	0.41	115	0
2	6	55	38	0.56	145	0
	7	68	47		185	5
	8	72	50	0.43	192	0
3	6	56	39	0.47	185	0
	7	55	38		210	9
	8	91	63	0.37	295	3
4	9	56	39	0.55	200	10
	10	78	54	0.53	300	0
5	11	55	38	0.62	225	0
	12	65	45		280	0
	13	—	—	0.54		
6	56	88	61	0.40	520	0
		92	64	0.38	450	0
7	74	99	69		445	4
		94	65	0.40	420	5
8	97	89	62	0.41	425	5
		88	61	0.41	405	0
9	99	95	66		305	7
		99	69	0.33	230	4
10	104	121	84	0.39	520	8
		114	79	0.38	640	3
11	134	117	81	0.40	410	0
		115	80	0.40	405	0
12	150	109	76	0.39	400	0
		108	75	0.39	520	0
13	150	111	77	0.39	400	0
		109	76	0.37	365	0
14	184	122	85	0.36	635	4
		111	77	0.42	490	10
15	211	104	72	0.42	500	0
		115	80	0.40	405	0
16	212	144	100	0.29	590	7
		151	105		460	2
17	224	147	102	0.28	455	7
		147	102		380	8
18	238	176	122	0.24	460	0
		181	126	0.24	365	4
19	255	127	88	0.40	675	0
		140	97	0.39	610	0

(Table 3, cont.)

Case	Age in days	True endogenous C_{CR}		Plasma creatinine conc. mg per 100/ml	Diuresis ml/24 h.	Urine loss in per cent of diuresis
		lit./24 h./1.73 sq. m.	ml/min./1.73 sq. m.			
20	266	121	84	0.35	500	0
		106	74	0.37	315	0
21	279	121	84		325	0
		130	90	0.40	330	3
22	279	132	92		230	0
		154	107	0.32	355	0
23	433	117	81	0.42	115	0
		119	83	0.41	200	0
24	651	117	81	0.36	485	0
		114	79		660	2
25	766	227	158	0.33	340	0
		200	139	0.36	330	0
26	772	168	117		410	0
		161	112	0.27	410	0
27	1671	162	113		660	
		173	120	0.38	780	
28 ¹	1714	207	144		700	
		202	140	0.36	620	
29	1843	157	109	0.45	920	
		145	101	0.45	690	
30 ¹	2064	137	95	0.46	530	
		142	99		610	
31	2194	181	126	0.35	610	
		219	152	0.41	730	
32	2415	145	101		410	
		125	87	0.58	440	
33	2519	153	106	0.45	375	
		164	114		445	
34	3250	151	105	0.67	660	
		140	97	0.66	730	
35	4218	153	106	0.62	610	
		154	107	0.68	740	
36	4251	134	93	0.64	820	
		151	105	0.54	1000	
37	4298	177	123	0.62	920	
		181	126	0.60	790	
38	5049	173	120		1350	
		171	119	0.82	1625	

¹ The 24-hour periods were not consecutive.

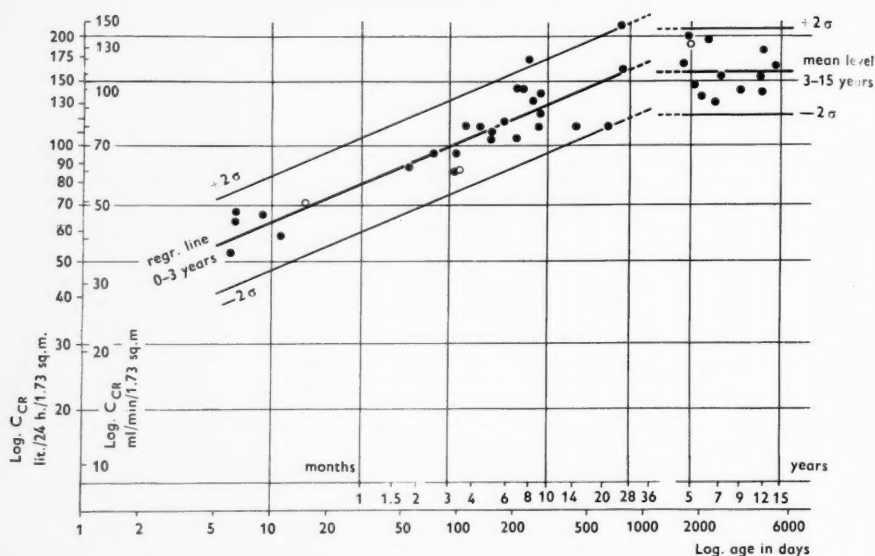


Fig. 1. The 24-hour true endogenous creatinine clearance corrected to 1.73 sq.m. in relation to age in days. Logarithmic transformations.

Filled circles: arithmetic mean of two determinations. Open circles: One single clearance determination performed. These cases have not been used in the calculation of the regression line and mean level.

The regression line for children < 3 years was: $\log y = 0.209 \log x + 1.45$; $y = \text{ml/min./1.73 sq.m.}$; $x = \text{age in days}$; $r = 0.90 \pm 0.04$; s.d. around regression line = $0.066 \log \text{ ml/min./1.73 sq.m.}$; $n = 26$.

The values for children > 3 years were: mean 2.05 ± 0.017 ; s.d. = $0.059 \log \text{ ml/min./1.73 sq.m.}$; $n = 12$.

per cent in the younger age group (0-3 years) and 6.7 per cent in the older (3-14 years) (Table 2). The small variations of the clearance values indicate that both the collection of urine and the estimation of the loss were correct enough for clinical use. The accumulated amount of creatinine calculated to have been excreted in the urine that was lost to the pad, was 1.6 per cent of the total accumulated creatinine excretion.

The variation of the plasma creatinine level in samples obtained on different days was small as in adults (Table 3). The error in one plasma creatinine value was 0.025 mg per 100 ml. (Table 2). This error

includes both the physiological variation and the error of analysis. The variations during the course of the day were not investigated, but since they have been found to be small in adults on a diet free from meat (1, 7), this was also assumed true in children.

In the above calculations the five youngest cases have been omitted. In these cases the technique used was assumed to give less representative values of C_{CR} than in older patients, partly because of the low diuresis, partly because of the change in both C_{CR} and plasma creatinine concentration observed during the period of investigation (Table 3). Because of

these circumstances it was felt to be correct to use three consecutive clearance values, where available, in the calculation of the mean C_{CR} in these infants.

II. Change in C_{CR} with increasing age.

All clearance values, expressed as ml/min. and lit./24 hours are given in (Table 3), after correction to standard body surface area. The mean values of these determinations have been plotted against age on a double logarithmic scale. (Fig. 1.)

For practical reasons the clearance values were plotted along a logarithmic time axis. Because of the very rapid increase in the clearance during the first weeks of life and, more generally, because of the approximately logarithmic growth during infancy, such a manipulation would seem to be justified.

A definite skewness in the clearance data in the direction of higher values was observed throughout the material. Hence, the clearance values were also transformed into logarithms in order to obtain as accurate and small limits of variation as possible around the regression line. This would tend to facilitate the later evaluation of pathological data. The effect of the transformation, however, was not so strong since, numerically, the clearance values were all rather large and were limited to a small range.

The GFR, estimated by mannitol or inulin (11, 20) has been shown to be within the adult range in all children between the ages of 2 and 3 years, when compared on a basis of body surface area; thus a regression line was calculated for the cases below the age of three years and a mean level for

the cases over this age. There is an approximately linear increase of the C_{CR} (with the logarithmic transformation used) up to an age of about 1-3 years, at which time stable values, lying within the 2 δ -limits of 85-146 ml/min./1.73 sq.m, seem to be reached. These limits were obtained from the standard deviation and mean of the logarithmic values. If, instead, these parameters were calculated from the original clearance values—as done in most papers on the subject—a mean of 113 ml/min./1.73 sq.m. and 2 δ -limits of 81-145 ml/min./1.73 sq.m. were obtained.

In Fig. 2 clearance values obtained from 7 other authors, who have used mannitol or inulin as a test substance, have been plotted together with the regression line, the mean level and 2 δ -limits of the values found in the present investigation. It is evident that the regression line makes an approximate mean of the values of the other investigations. In Friederiszick's series (11) the variation of the values in children below three years of age seems to be similar to that found by the present author; in other series the variation seems to be larger.

The clearance values given by Vesterdal & Tudvad (23) for infants during the first 10 days of life lie considerably below the lower 2 δ -limit found in the present investigation, as do also three of the values obtained by Dean & McCance (9) during the second day of life. Because of the extremely low diuresis, clearance values obtained during the first few days of life will likely be unreliable both in short and long term experiments.

The 24-hour inulin clearances obtained by Sirota, Baldwin & Villarreal (21) in 14 male subjects between the ages of 18

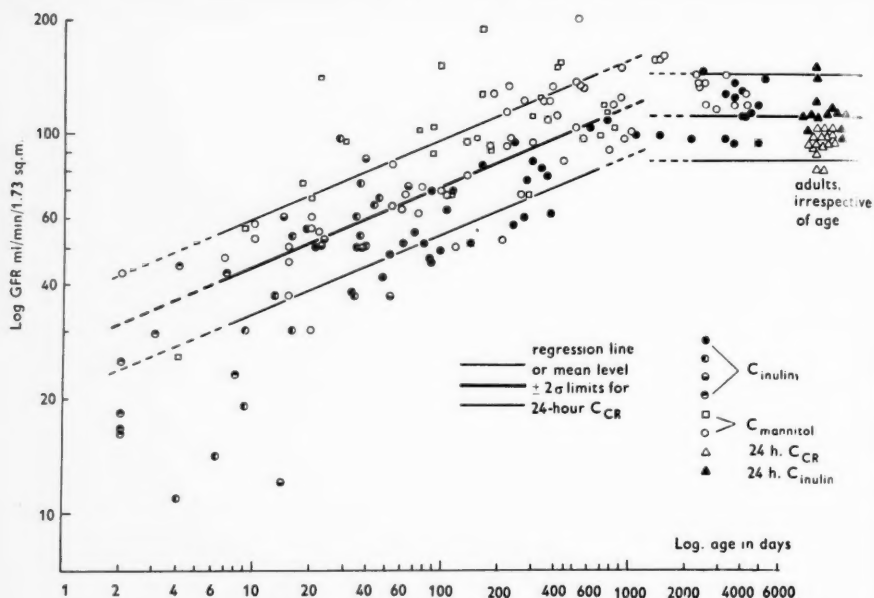


Fig. 2. Regression line and mean level with two σ -limits for the 24-hour C_{CR} in relation to GFR found by different authors in infants, children and adults. ● Friederiszick (11); ○ Versterdal & Tudvad (23) (Birth weight > 3010 g); ◐ Versterdal & Tudvad (23) (Birth weight 2500-3000 g); ◑ Dean & McCance (9); □ West, Smith & Chasis (25); ○ Rubin, Bruck & Rapoport (20); △ Camara, Arn, Reimer & Newburgh (7); ▲ Sirota, Baldwin & Villarreal (21).

and 50 years show a good agreement with the C_{CR} found in the older children (Fig. 2.) The 24-hour creatinine "chromogen" clearances, obtained by Camara *et al.* (7) were lower than the true creatinine clearance found in this investigation; a result which was expected, (Fig. 2.)

The advantage of using the 24-hour true endogenous creatinine clearance for estimation of GFR, besides causing less discomfort to the patient, is that the GFR is determined under more physiological conditions than are short term clearances. Thus the possible effect on GFR of massive hydration, emotion and pain (2, 6, 10, 18, 21, 23) are largely avoided. The limitation of using creatinine clearance as a

measurement of GFR lies in the fact that in renal failure C_{CR} , because of tubular secretion of creatinine, often is higher than C_{IN} (5, 14, 16, 17, 19). However, as pointed out by de Wardener (24), the larger errors are found at the low clearance values, where they are less important.

An interesting observation bearing upon the evaluation of the high $C_{CR}:C_{IN}$ ratio in some patients with renal insufficiency is that made by Calcagno *et al.* (6). These authors found that in small infants with a low C_{CR} , water diuresis caused a marked augmentation of the $C_{CR}:C_{IN}$ ratio, possibly due to tubular secretion of creatinine. It is not known whether hydration has the same effect upon creatinine excretion in

patients with low C_{CR} due to renal insufficiency, but if it has, the 24-hour C_{CR} can be supposed to equal C_{IN} in chronic renal disease more closely than the short-term C_{CR} does. This possibility however, deserves experimental support.

Summary

The 24-hour true endogenous creatinine clearance was determined in 38 children without known renal disease. When meat was excluded from the diet the C_{CR} and the plasma creatinine values were very stable from day to day. It seems sufficient

in routine clinical work to determine the creatinine excretion in one 48 hour period and to perform only one estimation of the plasma creatinine level.

The C_{CR} was found to increase up to the age of between one and three years, when stable values seemed to be reached. In children over three years of age the C_{CR} varied between 85 and 146 ml/min/1.73 sq.m. (122-210 lit./24 h./1.73 sq.m.).

The clearance values obtained show a good agreement with those obtained by other authors using inulin or mannitol as a test substance.

La clearance nyctémérale de la créatinine endogène spécifique chez des nourrissons et des enfants sans maladie rénale connue.

L'auteur a déterminé la clearance nyctémérale de la créatinine endogène spécifique, chez 38 enfants, sans maladie rénale connue.

Au cours de l'administration d'un régime sans viande, la clearance de la créatinine endogène spécifique est stable d'un jour à l'autre. Pour le travail de routine clinique, il suffit, semble-t-il, de mesurer la quantité de créatinine éliminée pendant 48 heures et de déterminer, une seule fois, le niveau de la créatinine plasmatique.

La clearance de la créatinine augmente progressivement jusqu'à l'âge de 1 à 3 ans; à cet âge il semble bien que les valeurs soient stables.

Chez les enfants âgés de plus de trois ans, la clearance de la créatinine varie entre 85 et 146 ml./min./1.73 m² (122-210 L./24 h./1.73 m²).

Ces valeurs de la clearance de la créatinine spécifique sont analogues à celles obtenues par d'autres auteurs qui ont utilisé l'inuline ou le mannitol pour déterminer la clearance.

Die spezifische endogene 24-stündliche Creatinin-Clearance von Säuglingen und Kindern ohne Nierenerkrankung.

Die 24-stündliche spezifische endogene Creatinin-Clearance wurde von 38 Kindern ohne bekannte Nierenerkrankung bestimmt.

Wenn Fleisch aus der Nahrung eliminiert wird, sind Creatinin-Clearance und Plasma-Creatinin-Werte von Tag zu Tag sehr stabil. Für die klinische Routinarbeit erscheint es genügend, die Creatinin-Ausscheidung während eines Zeit-

raums von 48 Stunden und nur einmal den Plasma-Creatinin-Spiegel zu bestimmen.

Die Creatinin-Clearance stieg bis zu einem Alter von 1-3 Jahren, wo konstante Werte erreicht wurden.

Bei Kindern über 3 Jahren schwankte die Creatinin-Clearance zwischen 85 und 146 ml/min/1.73 m² (122-210 L/24 h/1.73 m²).

Die Clearance-Werte stimmen gut mit denen anderer Autoren, die Inulin und Mannitol als Testsubstanzen verwendet haben, überein.

24-horas clearance de la verdadera creatinina endógena en lactantes y niños sin enfermedad renal.

El clearance de la verdadera creatinina endógena en las 24 horas, fué determinado en 38 niños sin enfermedad renal conocida.

Cuando se hubo excluido la carne de las dietas, los valores del C_{CR} y la creatinina plasmática se mostraron muy estables día a día. Al parecer, sería suficiente, para el manejo clínico de rutina, con una determinación de la excreción de creatinina en un período de 48 horas y una sola determinación del nivel de creatinina en plasma.

Se halló que el C_{CR} aumenta progresivamente hasta los 1 a 3 años, edad en que son alcanzados valores estables.

En los niños de más de 3 años, el C_{CR} varió entre 85 y 146 cc./min. por 1.73 m² o sea, de 122 a 210 Lts. por 1.73 m² en las 24 horas.

Los valores de clearance obtenidos se muestran en correspondencia con las cifras obtenidas por otros autores utilizando inulina o manitol como sustancia test.

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Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
Sweden

Cytogenetical Observations in Mongolism¹

by J. A. BÖÖK, M. FRACCARO and J. LINDSTEN

The development of cytological and cell culture techniques by which human chromosomes can be subjected to detailed studies has been one of the most important achievements in medical genetics during the past few years. Exact counts of the number of chromosomes of human lung fibroblasts derived from embryos and cultivated *in vitro* were first made by Tjio & Levan (1956). Of 265 cells from four different individuals all cells except four had 46 chromosomes.

These observations were confirmed and complemented by observations on human spermatocytes (first meiotic division) by Ford & Hamerton (1956). Of 188 cells from three different individuals 174 cells were classified as having 23 bivalents or 22 bivalents plus an XY pair and 14 cells as having 22 bivalents or fewer.

The somatic chromosome number of 46 was later confirmed with short time incubations of bone marrow cells by Ford *et al.* (1958) and with the cell culture technique by Tjio & Puck (1958a and b). More recently Chu & Giles (1959) examined cells from 34 individuals with the latter technique. All of them had 46 chromosomes in the examined tissues (mostly skin). By now a total of well over 3000 cells from some 100 individuals have

been analysed and the results are fairly consistent. Counts with the cell culture technique made in this laboratory are in complete agreement.

It seems likely that the observed deviations from the number of 46 are due mostly to technical difficulties. Ford *et al.* (1958) reported a rather wide range of variation in chromosome numbers. This may depend on the fact that no less than 14 of their 23 cases displayed some kind of hematological disease and spindle disturbances are known to occur *e.g.* in pernicious anemia (La Cour 1944). While 46 now appears confirmed as the normal or common somatic chromosome number in man there still remains some uncertainty concerning the chromosome number of the germinal epithelium.

Kodani (1958) examined testicular biopsies from eight Whites of whom seven had 46 and one 48 chromosomes and fifteen Japanese of whom nine had 46, one 47 and five 48 chromosomes. The numbers were consistent in Metaphase I as well as in spermatogonial mitoses. Kodani's interpretation was that, except for the XY-pair, there were consistently 22 normal bivalents. However, some individuals possessed a small supernumerary chromosome, single or in duplicate. It was slightly

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Fig. 1. Mitotic metaphase in a human male cell grown *in vitro*. The culture was derived from fetal brain. Aceto-orcein stain. Phase contrast. Photomicrograph 3,800 \times .

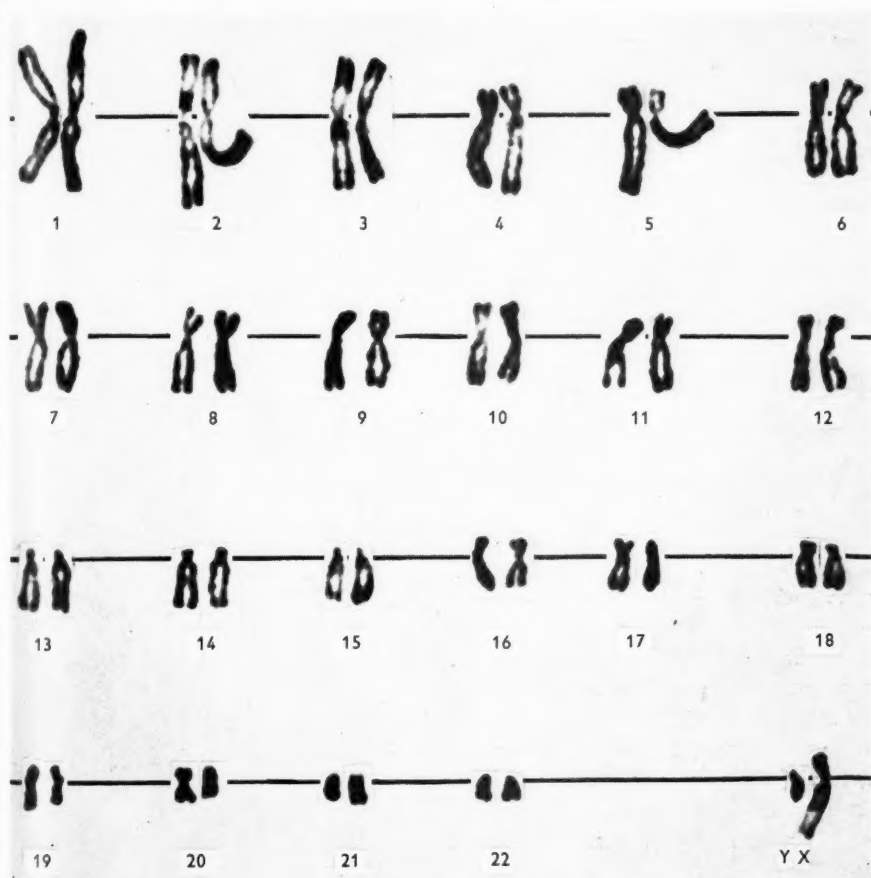


Fig. 2. The chromosomes of Fig. 1 arranged according to size and centromere position. The sex chromosomes have been marked YX.

smaller than the Y-chromosome but displayed the same staining properties. Feulgen squash preparations were used. For the time being it is not known if these 47th and 48th chromosomes are of the accessory type (cf. Müntzing 1954) or homologous with those of the normal complement. There is not necessarily a discrepancy between these observations and those on somatic cells. Accessory

chromosomes which are more or less restricted to the germinal epithelium have been described in other organisms e.g. in the flatworm *Polycelis tenuis* (Melander 1950). It should be kept in mind that chromosome studies in man are just beginning and variations in numbers as well as in morphology and structure are to be expected here as in other more thoroughly studied species.



Fig. 3. Mitotic metaphase in a human female cell grown *in vitro*. The culture was derived from a bone marrow biopsy. Aceto-orcein stain. Phase contrast. Photomicrograph 3,000 \times .

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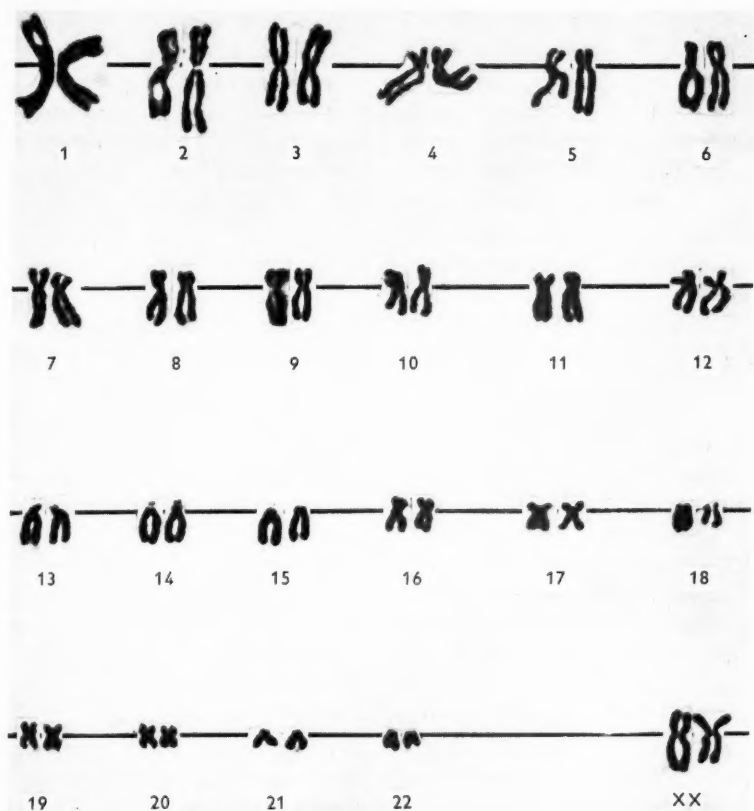


Fig. 4. The chromosomes of Fig. 3 arranged according to size and centromere position. The sex chromosomes have been marked XX.

A first tentative human idiogram was given by Tjio & Levan (1956) who described 10 chromosomes with median-submedian centromere (arm index 1-1.9), 10 with subterminal centromere (arm index 2-4.9) and 3 with near subterminal centromere (arm index > 5). In a later paper by Tjio & Puck (1958) a more detailed and revised idiogram was outlined. A similar idiogram has been published by Chu & Giles (1959). There are some discrepancies

largely due to the difficulty in distinguishing between some of the medium sized chromosomes with median or submedian centromeres. Only a few of the chromosomes are morphologically distinct. Further studies are necessary before each chromosome can be given its special designation. The results of our studies of the normal karyotype with the cell culture technique using fetal material is entirely in agreement with those reviewed

here. Photographs of a normal male and female chromosome complement are shown in Figs. 1-4.

While studies of the karyotype in various pathological conditions apparently have started more or less independently in several laboratories, Lejeune *et al.* (1959a) were the first to report the finding of 47 chromosomes in 3 patients with mongolism. Other findings of differences in chromosome numbers have been related to unexplained results of the determinations of "nuclear sex chromatin" according to Barr & Bertram (1949). Jacobs & Strong (1959) first reported a patient with gonadal dysgenesis of the Klinefelter type having 47 chromosomes. This was interpreted as an intersexual state of the XXY type. Ford, Jones *et al.* (1959) and Fraccaro *et al.* (1959) reported patients with gonadal dysgenesis of the Turner type with 45 chromosomes which was interpreted as an XO type. It is possible that some such individuals are true mosaics of the XXY/XX or XX/XO type as indicated by the finding of two different karyotypes in the bone marrow of the same individual (Ford, Polani *et al.* 1959, Ford, Harnden *et al.* 1959).

Other reports on the somatic chromosomes in mongolism have appeared recently. Jacobs *et al.* (1959) confirmed the results of Lejeune *et al.* and reported 3 males and 3 females with mongolism, all having 47 chromosomes. Further confirmation was given by Ford, Jones *et al.* (1959) who found a patient with mongolism and gonadal dysgenesis of the Klinefelter type. This individual was shown to have the expected 48 chromosomes, *i.e.* 44 plus XXY and a small extra chromosome. Lejeune *et al.* (1959b) have now reported

a total of 5 males and 4 females with mongolism all having 47 chromosomes.

There appears to be general agreement that the 47th chromosome present in the somatic cells of patients with mongolism belongs to the category of the two smallest pairs. It was described by Lejeune *et al.* (1959b) as "Un petit chromosome télacentrique surnuméraire" and by Jacobs *et al.* (1959) as "an acrocentric chromosome in the smallest size range". The rest of the chromosome complement appeared normal.

The British authors have all used short time incubations of sternal punctates and colchicine pre-treatment whereas cell cultures of biopsies taken from *fascia lata* were used by Lejeune *et al.* (1959a and b).

During the current year, studies of the normal human karyotype and its possible variations in different congenital malformations and syndromes have been carried out in this laboratory by continuous cultivation of somatic cells *in vitro*. Chromosome counts in mongolism have shown the number of 47 to be characteristic, thus confirming the results of others mentioned above. In one patient the important fact was established that the chromosome complements of cells derived from the bone marrow were identical with those derived from the skin. In addition, we have observed that subcultured cells retained a modal chromosome number of 47 through several transfers (cf. Table 1).

Cell Culture Methods

Bone marrow

The punctate was transferred directly into a sterile siliconised test tube containing 3 ml of heparinized culture medium. The medium

TABLE 1. *Types of cell cultures which have been cytologically analysed in three patients with mongolism. (—) unsuccessful culture.*

Patient No.	Bone marrow		Skin	
	Primary	Transfer no.	Primary	Transfer no.
1 (male)	+	5	—	—
2 (male)	+	4	+	3
3 (female)	—	—	+	3

for bone marrow cultures consisted of a mixture of 40 per cent human serum, 30 per cent medium 199 (Difco laboratories, Detroit), 30 per cent Hanks' balanced salt solution to which 5 ml of bovine embryo extract EE 20 (Difco) were added for every 100 ml. Penicillin and streptomycin were added routinely to the medium.

The biopsies can be stored at 4°C before shipment. The longest transportation with a successful culture result was about 48 hours. Before culturing the cell density was checked in a Bürker chamber.

About 1 ml of the suspension was poured into a sterile Petri dish (60 mm) containing a coverslip and another 2 ml of fresh medium was added. The cultures were kept in a humidified atmosphere of 5 per cent CO₂ in air at 37°C. After two or three days the coverslip was moved to a new Petri dish with fresh medium. Cells growing on the bottom of the Petri dish may be trypsinized and subcultured. The medium was changed every third or fourth day. Marked growth was observed usually after 10–15 days. For the chromosome preparations it is important to have only a moderate number of cells on the coverslip.

To obtain a large number of mitoses we have found it useful to change the medium 12–18 hours before making the preparations. For hypotonic treatment the coverslip was transferred to a 0.7 per cent sodium citrate solution prewarmed to 37°C and kept at room temperature for 10 minutes. The cells were fixed and stained in a solution of 2 per cent natural orcein (Gurr) in 50–60

per cent acetic acid. After one or two minutes the coverslip was placed on a microscope slide and superfluous fluid removed with filter paper. Squashing was made cautiously by light manual pressure and repeated until a good result was observed in the microscope.

Skin

The skin biopsies were collected in a culture medium consisting of 20 per cent human serum, 35 per cent Medium 199, 5 per cent bovine embryo extract EE 20 and 40 per cent Hanks' balanced salt solution.

The specimens were cut with a pair of sharp scissors into very small fragments. The cells were dispersed by treatment with 0.08 per cent trypsin (Difco 1:250) in Hanks' balanced salt solution for about 60 minutes at 37°C. The cell suspension obtained by this procedure and remaining tissue fragments were handled in the same way as described above. With this technique it may sometimes take up to 4 weeks before appreciable growth is obtained.

Case Reports

Patient No. 1. Fred M., male born in 1948. His father was born in 1913 and his mother in 1908. He had one healthy brother, born in 1941. The father was an alcohol addict and the mother went through a short psychotic episode in connection with the birth of the patient. He has spent all his time in different institutions. He started to walk at the age of 6 years but has never talked, has shown a lively disposition and is relatively easy to handle.

At the examination in 1959 no interpersonal contact was possible. However, he showed some interest and was able to play with simple toys. The mental defect was very severe (low-grade idiocy).

Head circumference 50 cm, head length 16.5 cm, head breadth 13.5 cm, cephalic index 82, height 119 cm, weight 21 kg. He had no typical epicanthic folds. The tongue was fissured and there was bilateral brachy-

dactyly and marked hyperextensibility of the finger joints. He had no transverse crease. The skin was dry and ichthyotic. There were no physical signs of heart disorder and no cyanosis. Both testes were undescended and located in the groins. The rest of the routine physical and neurological examination was negative.

A biopsy was taken from bone marrow (Dr. B. Bille) (cf. Table 1).

Diagnosis: Mongolism.

Patient No. 2. Tord M., male born in 1940. His father was born in 1909 and his mother in 1902. He had one healthy and normal brother born in 1934. Both parents were healthy and normal. The patient walked at 2 years and talked a few words at 3-4 years. Since he was 7 he was said to have rather regressed. He was looked after at home until he was 17 when he gradually became more difficult to handle and was therefore admitted to the Vipeholm Hospital at Lund.

On examination in 1959 he had a very severe mental defect (low-grade idiocy) with practically no interpersonal contact.

His head circumference was 53 cm, head length 18 cm, head breadth 14 cm, cephalic index 78, height 163.5 cm, weight 51.5 kg. He had epicanthic eyefolds on both sides. The tongue was large and of the *scrotalis* type. There was bilateral brachydactyly and hyperextensibility of the finger joints. Typical transverse creases were found in both palms. The skin was dry and ichthyotic. The malformed chest was of the *carinatus* type. There were no physical signs of congenital heart disorder. His hands and feet were markedly cyanotic. Both testes were descended and of normal size. Other secondary sex characteristics were normal. Further routine physical and neurological examinations showed no apparent abnormalities.

Biopsies were taken from bone marrow and skin (Dr. S. Rayner) (cf. Table 1).

Diagnosis: Mongolism.

Patient No. 3. Kerstin N., female born in 1929. Her father was born in 1888 and her mother in 1885. She was a single child.

She has been mentally retarded since birth and was taken care of in her home until 1939 when she was admitted to a colony for the feeble-minded. Because she became aggressive and destructive she was transferred to the Vipeholm Hospital in 1950.

At the examination in 1959 she displayed a very severe mental defect (low-grade idiocy). She could not talk but apparently understood some simple commands. Otherwise she took no interest and no interpersonal contact could be established.

Her head circumference was 50 cm, head length 16.5 cm, head breadth 12.5 cm, cephalic index 76, height 144 cm and weight 41.5 kg. She had typical epicanthic folds on both eyes. The tongue was large and of the *scrotalis* type. She had bilateral brachydactyly and hyperextensibility of the finger joints. A transverse crease was observed in her right palm. The skin was coarse and dry. On physical examination her heart showed signs of congenital heart disorder. Her hands and feet were cyanotic. She first menstruated at the age of 23 years. Secondary sex characteristics were underdeveloped. No special gynecological examination was made. Further routine physical and neurological examinations showed no apparent abnormalities.

Biopsies were taken from bone marrow and skin (Dr. S. Rayner) (cf. Table 1).

Diagnosis: Mongolism.

Cytology

The normal chromosome complement

All chromosome preparations have been made as described above (p. 459) and without the use of colchicine pre-treatment. Figs. 1-4 show photomicrographs of the male and female chromosome complements as taken from cells grown *in vitro*. In Figs. 2 and 4 the 22 autosomal pairs have been arranged according to their size and the position of the centomere. The sex chromosomes are shown



Fig. 5. Mitotic metaphase in a cell grown *in vitro* from Patient No. 1 (male) showing 47 chromosomes. The culture was derived from a bone marrow biopsy. Aceto-orcein stain. Phase contrast. Photomicrograph 4,500 \times .

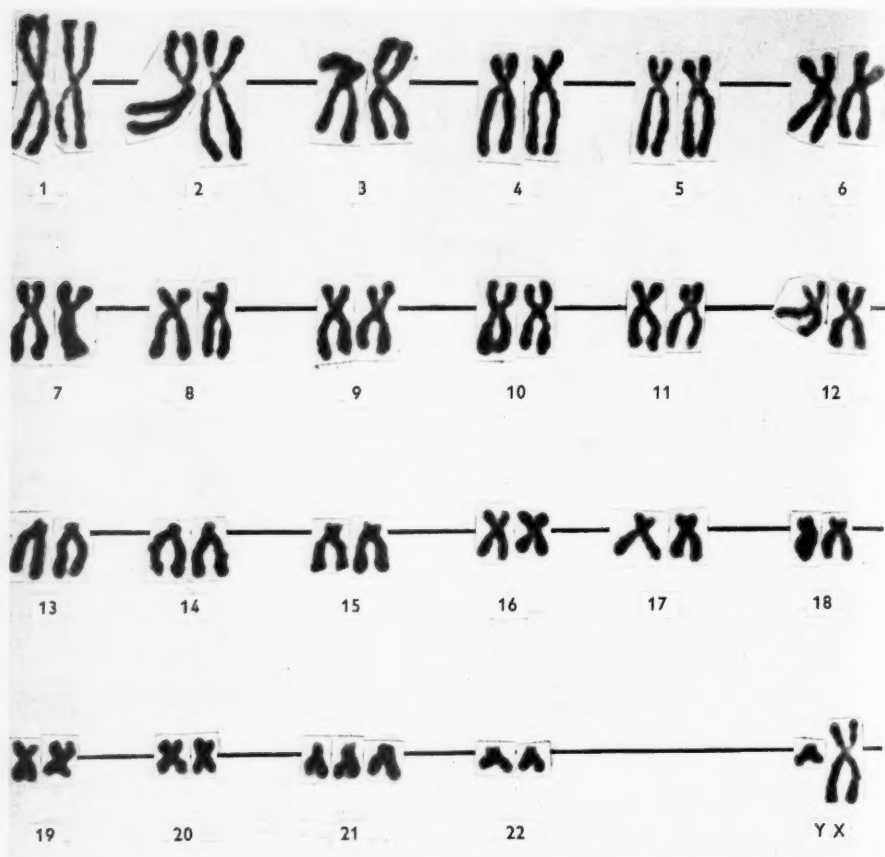


Fig. 6. The chromosomes of Fig. 5 arranged according to size and centromere position. The 47th chromosome has been placed at No. 21.

separately. There are no differences between the autosomes of a male and female set. The chromosomes Number 1 and 3 are large with a median centromere. No. 2 has a submedian centromere while in Nos. 4 and 5 they are subterminal.

The group of medium sized autosomes (Nos. 6-12) have median or submedian centromeres. Nos. 13, 14 and 15 are acrocentric chromosomes of approximately the same size. Nos. 16, 17 and 18 have

median, submedian and subterminal centromeres respectively while in Nos. 19 and 20 they are median. The last two autosomes, Nos. 21 and 22, are small acrocentric chromosomes, No. 21 being slightly larger than No. 22. The male and female chromosome complements can easily be differentiated. The diploid male complement always contains five small acrocentric chromosomes one of which is the Y-chromosome whereas the diploid female



Fig. 7. Mitotic metaphase in a cell grown *in vitro* from Patient No. 3 (female) showing 47 chromosomes. The culture was derived from a skin biopsy. Aceto-orcein stain. Phase contrast. Photomicrograph 3,500 \times .

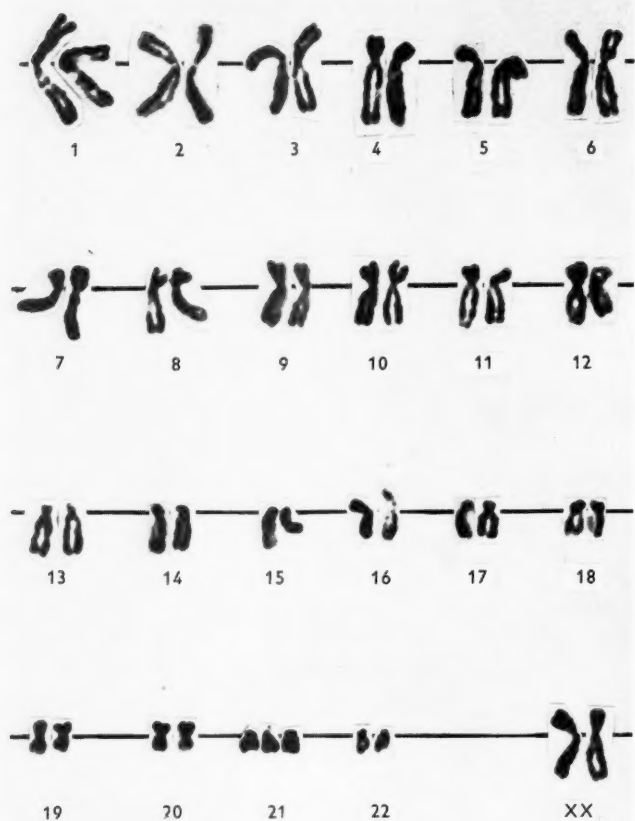


Fig. 8. The chromosomes of Fig. 7 arranged according to size and centromere position. The 47th chromosome has been placed at No. 21.

complement has only four such chromosomes. The X-chromosome can be identified tentatively by matching the chromosomes of the male complement. One medium sized chromosome will remain unmatched. A tentative appraisal of the X-chromosome according to its size should place it between autosomes Nos. 6 and 7. In some cells we have observed two pairs of acrocentric chromosomes having two chromatic bodies apparently connected

with the short arms by thin chromatin threads. With the Feulgen stain we have so far not been able to decide whether this small region located between the chromatic body and the centromere is heterochromatic or not. One of the pairs belonged to the group 13-15 and the other is likely to be pair No. 21. These satellite-like formations were best seen in the most successful preparations and in cells in late prophase.



Fig. 9. Detail from a photomicrograph of a skin cell from Patient No. 2 in late prophase. The arrows point to three acrocentric chromosomes with satellite-like formations as described in the text.

The chromosome complement in mongolism

The chromosome complements of cells derived from a female and a male patient with mongolism is shown in Figs. 5-8. The 47th chromosome which was constantly found in these cells is acrocentric and approximately of the same size as No. 21. As mentioned previously chromosome No. 21 might have a morphologically distinct satellite. It is therefore of interest to note that we have observed, in some of the cells from the patients, three small acrocentric chromosomes with satellite-like formations (cf. Figs. 9 and 10). Thus, while mongolism might be caused by trisomy involving autosome No. 21 a definite conclusion cannot, of course, be based on morphological similarities alone.

The rest of the chromosome complement in cells derived from the patients with mongolism was not found to be different from that observed in cells derived from normal individuals.

Discussion

The important discovery by Lejeune *et al.* (1959a and b) that individuals affected with mongolism have a characteristic karyotype has been confirmed in this laboratory with a similar technique but in cells derived from bone marrow and skin. Up to now a total of 10 males, 8 females and one intersex with mongolism have been reported. Insofar as the number of chromosomes, 47, is concerned the results are consistent enough to assume that this is characteristic, at least for the majority of these patients. It would, however, be premature to claim, at this juncture, that the etiology of mongolism was definitely solved. This discovery raises a number of new questions. It cannot as yet be decided whether or not the 47th chromosome is a normal homologue of the haploid set or structurally different.

Aneuploid conditions have been found quite frequently in plants, but rarely in animals. In *Drosophila melanogaster* trisomy of the large autosomes is always lethal at an early stage while the presence of three 4th chromosomes reduces viability only slightly (Li 1927). These flies (triplo-IV) have small eyes, narrow pointed wings, darker body colour and a suppressed trident pattern (Morgan *et al.* 1925). Conditions may, however, be quite different in different species and it remains to be seen whether aneuploidy or structural variations of the human chromosomes is an important cause of genetic variation.

Nevertheless it is significant that a new type of genetical pathology has been demonstrated where a kind of block

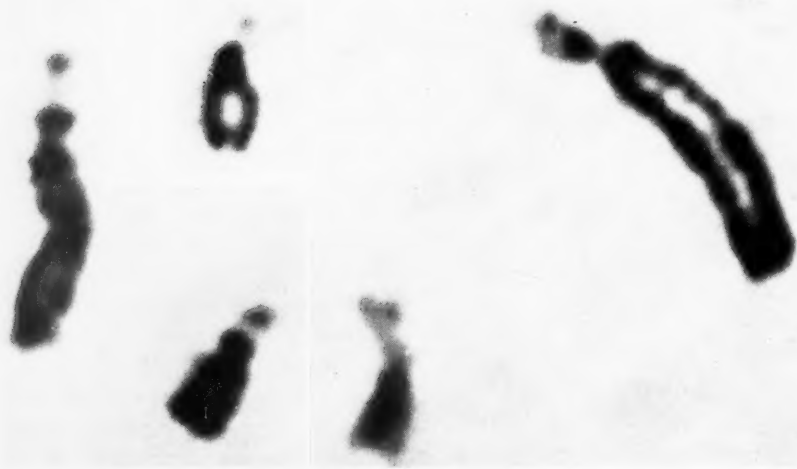


Fig. 10. Photographic enlargement of the three chromosomes marked in Fig. 9 and the pair of large acrocentric chromosomes with satellite-like formations.

genetical difference can be actually seen in the microscope.

If the 47th chromosome found in patients with mongolism is the primary cause of the abnormal development it is more likely to be a third homologue than an accessory chromosome. Single accessory chromosomes have not been observed to affect the viability of the organism in any striking way (Müntzing 1954).

As mentioned above, we have found some morphological evidence of trisomy. It is, however, necessary to study the behaviour of the 47th chromosome in meiosis and also the karyotype of the parents, siblings and children of patients with mongolism. Unfortunately male patients are very often sterile and so far we have not been able to obtain a testicular biopsy with active spermiogenesis. However, meiosis in mongolism has been studied previously by Mittwoch (1952) when the techniques available were less adequate.

Previous observations on mongolism with regard to high maternal age and relatively low risk of recurrence in the same sibship (cf. Penrose 1954, BööK & Reed 1950) could be explained by the occasional production, through non-disjunction, of egg cells containing 24 chromosomes. Also the fact that female patients are known who have given birth to normal as well as affected children (Lelong *et al.* 1949, Sawyer 1949, Forssman & Thysell 1957, Rehn 1957, Schlaug 1957 and Stiles 1958) is in agreement with the expected behaviour of such a chromosome complement during meiosis.

Finally we should like to emphasize that there may be other causes for the development of syndromes of the mongolism type. The number of individuals who have been studied in respect of their karyotypes is at present not large. It is therefore important that, in the future, all reports on karyotypes in human

pathological conditions should include clinical descriptions and the relevant genetical family data.

Summary

After a review of current work on chromosomal variations in man observations

on three patients with mongolism are described. Chromosome studies by the cell culture technique using cells from bone marrow and skin showed a modal number of 47. This confirms quite recent results reported by French and British workers. The type of the 47th chromosome is discussed briefly.

Après un exposé des investigations actuelles sur les variations du nombre chromosomique chez l'homme des observations faites sur trois malades mongoliens sont rapportées. Utilisant des cellules prélevées de moëlle osseuse et de peau les auteurs ont étudié les chromosomes par la culture de tissu et trouvé un nombre chromosomique de 47 chez ces malades. Ceci s'accorde avec des résultats récemment rapportés par des auteurs français et anglais. On discute également en résumé le type du 47ième chromosome.

Nach einer Übersicht über die jetzigen Untersuchungen von Chromosomvariationen im Menschen, werden Beobachtungen, die bei drei Patienten mit Mongolismus gemacht worden sind, beschrieben. Chromosomstudien mit Zellkulturtechnik und unter Anwendung von Zellen

von Knochenmark und Haut, gaben eine modale Anzahl von 47 Chromosomen bei diesen Patienten. Dieses Resultat steht im Einklang mit den neuesten französischen und englischen Forschungsergebnissen. Der Typus des 47. Chromosoms wird in Kürze dargelegt.

Después de una revisión de recientes trabajos sobre variaciones en cromosomas, se describen observaciones hechas en tres pacientes con mongolismo. Estudios de cromosomas a través de la técnica de cultura celular, usándose células de médula ósea y piel han mostrado un número modular de 47. Esto confirma resultados recientemente publicados por investigadores franceses e ingleses. Se discute brevemente el tipo del cromosoma 47.

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Institute for Medical Genetics
University of Uppsala
Uppsala
Sweden

The External Cranial Volume of Macro- and Microcephalic Children

by J. BALSLEV JØRGENSEN, E. PARIDON and F. QUADE

In this journal (*Acta pædiat.*, 48: 371, 1959) we have previously published the normal values of 'the external cranial volume' (ECV), stating that we had found this measurement to be more closely correlated with the weight of the child than with age or height. Now it lay near at hand to ask if the ECV might be useful in practice when diagnosing pathological conditions characterized by an abnormal size of the head. So we examined a small group of children from pediatric institutions in which the following clinical diagnoses had been made: hydrocephaly certain (two cases); hydrocephaly assumed (four cases); microcephaly assumed (three cases); microcephaly certain (two cases).

Furthermore we have included five children with mongolism as we thought it might be of interest to measure the size of the head in this condition.

In Fig. 1 the line in the middle shows the mean values for ECV in its relation to body weight, and the four others represent \pm and $-$ once and twice the standard deviation. The ECV values of the two children (A and B) with marked hydrocephaly were so large (2870 and 5200 cc) that they could not be contained within the framework of the illustration. Although the condition of these two children

can be diagnosed at a glance (Figs. 2 and 3) we have included them because we wanted to show that a well-pronounced hydrocephaly represents a deviation compared with which the normal variation is very narrow.

Of the four children (C, D, E, and F) who were under observation for macrocephaly, particularly for incipient hydrocephaly, three (C, E, and F) had ECV's on the line representing twice the standard deviation, while D fell outside this limit. The photos of C, D, and E are shown in Figs. 4, 5, and 6.

The three children (G, H, and J), who were suspected of being microcephalic, are shown in Figs. 7, 8 and 9. The ECV values of the first two are within the normal range, but J, whose head was somewhat narrow, presumably due to a premature closure of the sagittal suture, surprised us by having a volume clearly above normal.

Two children, K and L, who, for one thing, were deeply oligophrenic, and in whom the diagnosis of microcephaly was beyond doubt, had ECV values clearly below normal. K's picture is seen in Fig. 10.

The five mongoloid children, who are represented by cubes in the diagram, had

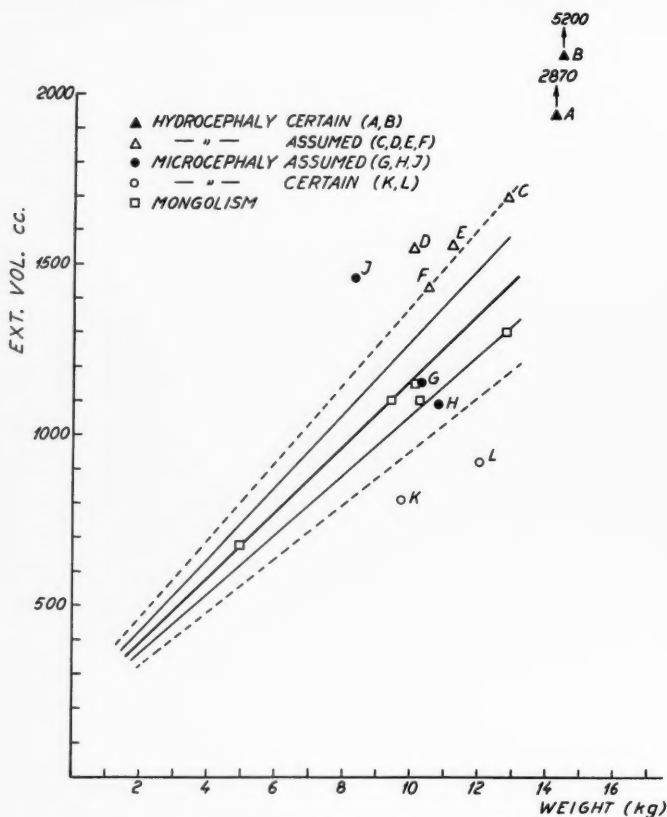


Fig. 1. External cranial volumes of sixteen children, shown in relation to the normal values.

all of them heads of a perfectly normal size.

The final estimation of the usefulness of the ECV must, of course, await further trial; still we venture to draw the following conclusions:

(1) The variation of the normal ECV is very small in comparison with the deviations found in clinically pronounced hydrocephaly. This fact justifies the hope that hydrocephaly in the early stages can be detected by measuring the ECV.

(2) If there is a clinically marked hydro- or microcephaly it is, of course, unnecessary for the diagnosis to measure the ECV, but the method may be useful in following variations in the condition.

(3) Of four children who had aroused clinical suspicion of incipient hydrocephaly, one was clearly above the normal range for ECV, and the rest had borderline values. In these cases the measurement can be said to have substantiated the clinical impression.



Fig. 2. Hydrocephalic child (A). ECV = 2870 cc.



Fig. 3. Hydrocephalic child (B). ECV = 5200 cc.



Fig. 4. Two-year-old boy (C) suspected of having an incipient hydrocephaly. ECV of borderline value.

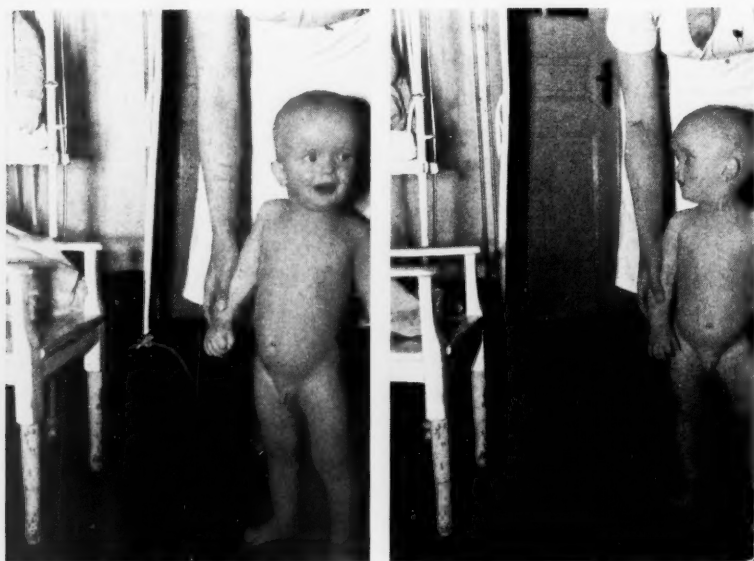


Fig. 5. Sixteen-month-old boy (D) suspected of having an incipient hydrocephaly. ECV clearly above normal.

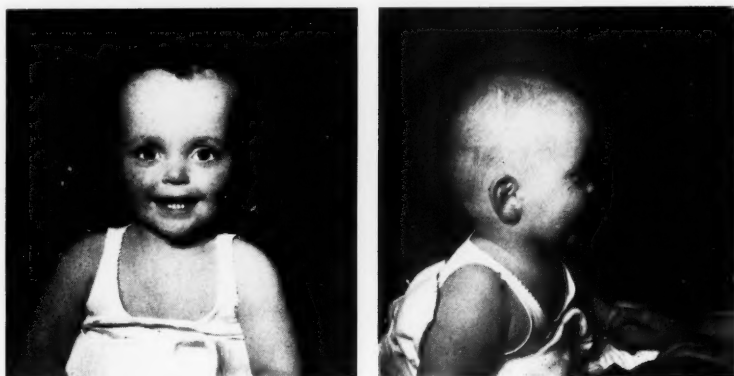


Fig. 6. One-year-old boy (E) with caput quadratum, suspected of being macrocephalic. ECV of borderline value.



Fig. 7. 2½-year-old girl (G) suspected of being microcephalic and oligophrenic. ECV normal.



Fig. 8. Three-year-old boy (H), oligophrenic, suspected of being microcephalic. ECV normal.



Fig. 9. Five-year-old boy (J), slightly oligophrenic, suspected of being microcephalic. An elevated ridge could be felt along the sagittal suture. ECV was, however, clearly above normal.



Fig. 10. Four-year-old girl (K), in whom oligophrenia and microcephaly was beyond doubt. ECV clearly below normal.

(4) Three children looked as if their heads were of less than normal size; two of them, however, had normal ECV-values, and the third was clearly macrocephalic. This goes to prove that the visual impression may be positively misleading, especially if the head is of a peculiar shape, as was the case with the macrocephalic child.

(5) Children with mongolism appear to have heads of normal size.

Acknowledgements

We are greatly indebted to Professor Oluf Andersen, M.D., Henning Andersen, M.D., and to Aksel Olsen, Chief Physician, for giving us permission to examine the children.

Summary

In order to evaluate the usefulness of measuring "the external cranial volume" (ECV: the volume of the part of the head which is above the glabella-inion plane) we

have examined a small group of children who, tentatively or finally, had been diagnosed as having an abnormal size of the head; furthermore, we have included a few cases of mongolism. The results seem to warrant the following conclusions: (1) The variation of the normal ECV is very small in comparison with the deviations found in clinically pronounced hydrocephaly. This fact justifies the hope that hydrocephaly in the early stages might be detected by measuring the ECV. (2) In clinically marked hydro- or microcephaly it is, of course, unnecessary to measure the ECV for diagnostic purposes, but the method may prove useful in following variations in the condition. (3) In the children suspected of incipient hydrocephaly, the measurement backed up the clinical suspicion. (4) Contrarily, normal or even elevated ECV values were found in three children who were under observation for microcephaly. (5) Five children with mongolism all had heads of a normal size.

Le volume crânien externe chez des enfants macro- ou microcéphaliques

Dans le but d'apprécier l'utilité du mesurage du volume crânien externe (V.C.E.), nous avons examiné un petit groupe d'enfants qui étaient soupçonnés ou qui avaient été reconnus avoir une tête de taille anormale. Nous y avons ajouté quelques cas de mongolisme. Les résultats semblent apporter les conclusions suivantes: 1) Les variations du V.C.E. normal sont minimes si on les compare avec les modifications observées dans les cas où l'hydrocéphalie est cliniquement accentuée. Ce fait justifie l'espoir que l'hydrocéphalie à ses premiers stades peut être détectée par la mesure du V.C.E. 2) Dans les cas où l'hydrocéphalie ou la microcéphalie est cliniquement décelable la mesure du V.C.E. est naturellement superflue pour assurer le diagnostic, mais cette méthode peut être utile pour apprécier les variations successives de ces états. 3) Pour les enfants chez qui l'on avait soupçonné une hydrocéphalie latente cette mesure renforça l'im-

pression clinique. 4) Par contre, des valeurs normales ou même élevées du V.C.E. furent trouvées chez trois enfants qui avaient été placés en observation pour microcéphalie. 5) Cinq enfants avec mongolisme présentèrent tous des têtes de taille normale.

Das äussere Schädelvolumen von Kindern mit Makro- und Mikrocephalie

Um die Brauchbarkeit der Bestimmung des äusseren Schädelvolumens auszuwerten, haben wir eine kleine Gruppe von Kindern, die verdächtig oder endgültig als im Besitz von abnormaler Kopfgrösse diagnostiziert worden waren, untersucht; ausserdem haben wir einige Fälle von Mongolismus in die Untersuchung einbezogen. Die Ergebnisse lassen folgende Schlussfolgerungen zu: 1. Die Variationen im Wert des normalen äusseren Schädelvolumens sind im Vergleich zu den Abweichungen bei ausgesprochenem klinischen Hydrocephalus sehr klein. Diese Tatsache rechtfertigt die Hoffnung,

dass Frühstadien von Hydrocephalus mit Hilfe der Bestimmung des äusseren Schädelvolumens entdeckt werden könnten. 2. Bei klinisch ausgesprochener Hydro- oder Mikrocephalie ist es natürlicherweise für diagnostische Zwecke überflüssig, das äussere Schädelvolumen zu bestimmen, aber die Methode könnte für die Verfolgung von Veränderungen bei diesen Zuständen von Nutzen sein. 3. Bei Kindern, bei denen ein beginnender Hydrocephalus verdächtig wurde, unterstützte die Volumbestimmung den klinischen Verdacht. 4. Im Gegensatz dazu fanden sich normale oder sogar erhöhte äussere Schädelvolumenwerte bei drei Kindern, welche wegen Mikrocephalie unter Beobachtung standen. 5. Fünf Kinder mit Mongolismus hatten ausnahmslos Köpfe von normaler Grösse.

El volumen craneano externo en niños micro- y macrocefálicos

Para valorar la utilidad de la medición del volumen craneano externo (E.C.V.) hemos exa-

minado un pequeño grupo de niños quienes, primaria o definitivamente, es habían diagnosticado como mostrando anomalías del volumen cefálico; hemos incluido, además, algunos casos de mongolismo. Los resultados parecen autorizar las siguientes conclusiones: 1. La variación del E.C.V. normal es muy pequeña si se la compara con las variaciones halladas en aquellas hidrocefalias muy marcadas clínicamente. Este hecho justifica la esperanza de que la hidrocefalia pueda ser detectada en los primeros momentos de la vida por la medida del E.C.V. 2. En las hidro- o microcefalias clínicamente muy acentuadas es, por supuesto, innecesaria la determinación del E.C.V. para su diagnóstico, pero puede ser útil para seguir las variaciones evolutivas. 3. En los niños con posible hidrocefalia incipiente, la determinación ratificó la sospecha clínica. 4. En tres niños bajo observación por microcefalia, fueron hallados, al contrario, valores normales, o aún elevados del E.C.V. 5. Los 5 niños mongólicos presentaron todas medidas cefálicas normales.

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Ostersøgade 20
Copenhagen
Denmark

From the Department of Bacteriology (Head: Prof. B. Malmgren) and the Department of Histology (Head: Prof. G. Häggqvist), Karolinska Institutet, Stockholm 60

Pulmonary Damage Caused by Oxygen Poisoning An Electron-Microscopic Study in Mice

by B. CEDERGREN, L. GYLLENSTEN, and J. WERSÄLL

Introduction

The toxic effects on animals and on man of oxygen in high concentrations have been recognized since the end of the 19th century (Bert 1878). A large number of publications have appeared on the general behaviour and pathology of experimental animals in atmospheres with high oxygen concentrations (Stadie *et al.* 1944, Bean 1945, Ohlsson 1947, Berger & Davenport 1950, Comroe & Dripps 1950). The literature on the morbid anatomy and histologic changes in the lungs in oxygen poisoning has recently been reviewed by Berfenstam *et al.* (1958).

Special interest has been focused on studies of the pulmonary effects of oxygen in high concentrations. This is because close similarities have been observed between the histologic features in the lungs of oxygen-poisoned animals and in the lungs of newborn infants, who have died of hyaline membrane disease (Clamann *et al.* 1940, Liebegott 1941, Bruns & Shields 1951, 1954, De & Anderson 1953, 1954, Berfenstam *et al.* 1954, 1958, Editorial in *The Lancet* 1958). It can be inferred from these investigations that hyaline mem-

branes may be caused or influenced by several factors, as may similar changes in the lungs of experimental animals. Among these factors are aspiration of amniotic fluid (Farber & Wilson 1932, Ahlström 1942, Blystad *et al.* 1951, Landing 1953), stress reactions and adrenal hormones (Bean & Johnson 1955, Bean 1956). Thus, oxygen poisoning cannot be the only cause of pulmonary hyaline membranes, and most probably is not even the main one. Despite this, experiments with oxygen-induced hyaline membranes have provided valuable information on the pathology and pathogenesis of the disease, as have recent histochemical investigations on the nature of the membranes.

The membranes are found in the alveolar ducts, respiratory bronchioles and alveoli of the affected lungs. They are strongly acidophilic and give an intensely positive reaction with the periodic-acid-Schiff technique, probably due to the presence of a carbohydrate (or polysaccharide) moiety containing a 1,2-glycol linkage (Gilmer & Hand 1955). They have been reported to contain blood proteins and fibrin (Gitlin & Craig 1956, Aikawa & Bruns 1956), traces of haemoglobin (Lynch *et al.* 1956), and blood cells (Potter 1953, Berfenstam *et al.* 1958). These state-

ments support the theory that hyaline membranes are composed of material which has escaped from the pulmonary circulation into the air spaces of the lung. The often conspicuous pulmonary oedema frequently associated with hyaline membranes and oxygen-intoxicated lungs (Potter 1953, Lendrum 1955, Penrod 1956, Aikawa & Bruns 1956) lends further support to this argument.

The mechanism of oxygen toxicity in general is not known. Recent studies of certain abnormalities in the postnatal development of premature human infants and experimental animals after oxygen exposure suggest that oxygen poisoning may produce alterations in membrane permeability (including capillary permeability), and that such alterations may be the cause of anomalies of the eye (Ashton 1957, Ashton *et al.* 1957) or brain (Gyllenstein 1959). These inferences are, however, only tentative and provide no conclusive evidence regarding the pathogenesis of oxygen-induced tissue injury.

Some results have been reported of electron-microscopic studies of lungs from oxygen-exposed animals, and from human subjects with hyaline membrane disease (Schulz 1956, 1957, 1958, van Breemen *et al.* 1957). No definite conclusions on the sub-microscopic pathogenesis of hyaline membrane disease or pulmonary oxygen damage have been reached in these studies.

The aim of the present investigation was to study the changes in the mouse lung after exposure to high concentrations of oxygen, with special reference to lesions of the alveolar walls.

Material and Methods

Altogether 60 male, inbred, adult C_3H mice (weighing about 20 g) were used.

Thirty-four animals were used for histologic and electron-microscopic investigations, 10 were used for bacteriologic study, and 16— not exposed to oxygen—served as controls. The mice to be exposed to oxygen were placed in an airtight incubator (volume 30 l), which was perfused with humidified oxygen at a flow of 0.5–1 liter per minute. The concentration of oxygen was 95–100 per cent; it was checked twice a day with an electromagnetic oxygen analyzer. The relative humidity was 80–90 per cent. The duration of oxygen exposure was 3–6 days. The mice were fed on a standard diet, with drinking water *ad libitum*.

In preparing the animals for biopsy, they were first anaesthetized by intraperitoneal injection of 0.5–0.8 ml of 0.5 per cent Numal (Roche). The lungs of the oxygen-exposed animals were fixed within 5–30 min. of removal of the animals from the incubator.

Specimens intended for light microscopy were injected with about 0.5 ml of 10 per cent formaldehyde intratracheally, the fixative being kept in the bronchial tree by ligating the trachea. After a few minutes, the lungs were removed and put in 10 per cent formaldehyde for further fixation. The specimens were embedded in paraffin. At least ten sections, 5 microns thick, were cut from the lungs of each animal. They were stained with haematoxylin and eosin, Weigert's resorcin-fuchsin for elastic fibres in combination with haematoxylin and van Gieson's stain, and the periodic-acid-Schiff (PAS) technique, all according to routine methods.

The lung specimens used for electron microscopy were fixed in 1 per cent osmium tetroxide solution, pH 7.2–7.3, in a veronal acetate buffer (Palade 1952, Sjöstrand 1953 and Rhodin 1954) at $+4^{\circ}\text{C}$. The fixative was injected intratracheally, about 0.5 ml in each animal, with very slight force. After about one minute, the thoracic cavity was opened and the lungs removed. The left large pulmonary lobe was put in 1 per cent osmium tetroxide solution for further fixation for 4 hours at $+4^{\circ}\text{C}$. A second lung lobe from each animal was cut with a razor blade into small slices, less than 1 mm thick;

these slices were also placed in a bottle with fixative for a further 4 hours. The whole lobe was later cut into small pieces during the dehydration in 70 per cent ethanol. Both methods apparently gave the same result. After fixation, the specimens were rinsed for half an hour in Tyrode solution.

Dehydration and embedding were performed according to the following schedule (Newman, Borysko & Swerdlow 1949).

70% ethanol + 0.2% phosphotungstic acid
1 hr, + 4°C.

95% ethanol + 0.2% phosphotungstic acid
2 hr, + 4°C.

Abs. ethanol + 0.2% phosphotungstic acid,
2 hr, + 4°C.

Abs. ethanol + 0.2% phosphotungstic acid
1 hr, room temp.

Monomer methacrylate (15% methyl-; 85%
butyl-; 0.1% benzoyl peroxide) 1 hr, room
temp.

Prepolymerization of the methacrylate preceded final polymerization at + 44°C.

The blocks were sectioned with glass knives on a Sjöstrand ultramicrotome (Sjöstrand 1953) and floated on 20 per cent ethanol. The sections were transferred to specimen grids covered with a formvar film. The microscope used was the Japanese instrument "Tronscope" (Akashi Ltd., Tokyo).

In order to ascertain to what extent accidental bacteria eventually contributed to development of the severe pulmonary damage in oxygen-intoxicated mice, a rough bacteriologic control was made. Ten animals were exposed to oxygen for 5 days. All of them were severely affected at the end of this period, as judged by their behaviour and the haemorrhagic and consolidated appearance of the lungs, and two died at the end of exposure. The surviving mice were anaesthetized by intraperitoneal injection of 1 ml of 0.5 per cent Numal. As soon as possible the animals were opened, using proper bacteriologic technique (burning the front of the mouse with a flame and using sterile forceps and scissors). The left large lung lobe was cut free at the hilus and put in a sterile mortar, where it was homogenized. The ho-

mogenate was inoculated in different bacteriologic media (blood-agar dish, chocolate-agar dish, thioglycolate broth, and broth with ascitic fluid). The media were observed daily for one week.

Results

After 2-3 days in oxygen, the animals became more or less affected, refusing food and water, keeping still in the cage and breathing slowly and deeply. During the 5th day, 4 out of 24 mice died. On the 6th day, 5 out of 16 died. Four of the animals exposed to oxygen for 5-6 days died within a few minutes of being transferred to air after the end of exposure. At *autopsy*, the lungs of mice exposed for 3 and 4 days showed small, scattered, dark-red patches. After 5-6 days in oxygen, all lungs showed changes of more or less pronounced development, at a considerable variation. Parts of the lungs appeared normal, whereas other parts were covered with small, dark-red patches, with a distinct tendency to confluence, resulting in bluish-red, consolidated, air-less masses, sometimes involving whole lobes.

Histologic Examinations

The great variation in pulmonary damage by oxygen intoxication was confirmed by the *histologic appearance of the lungs*. The degree and localization of the injury also varied from animal to animal.

After 3 days' stay in oxygen, only inconspicuous changes were found chiefly in the form of mild capillary stasis and slight alveolar exudation. After exposure for 3-4 days, the lesions were still relatively slight, consisting of areas with capillary dilatation and stasis, alveoli filled with a slightly acidophilic, PAS-positive exudate, pres-

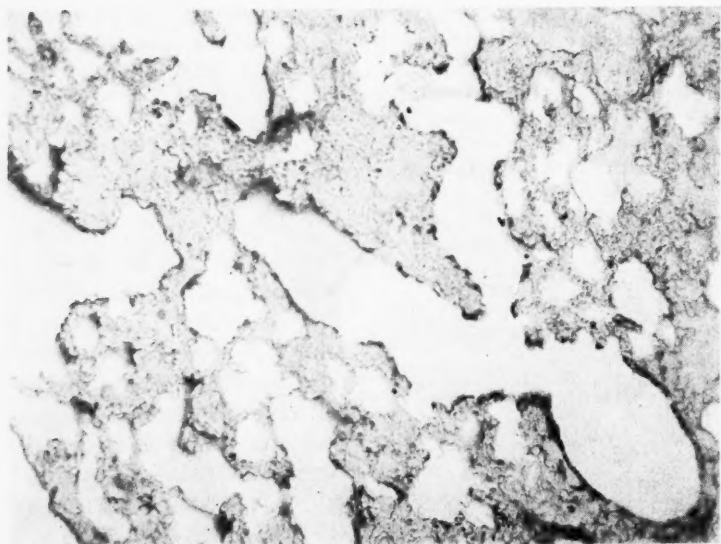


Fig. 1. Mouse lung after exposure to oxygen for 5 days. PAS reaction. Scattered PAS-positive membranes in bronchioles and alveolar ducts. Diffuse PAS-positive exudate in alveoli. 90 \times .

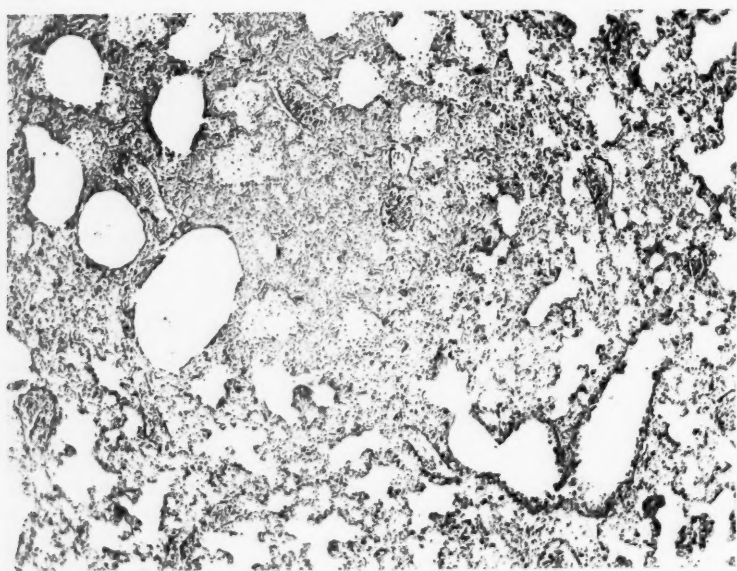


Fig. 2. Mouse lung after exposure to oxygen for 5 days. Consolidation and atelectasis, alternating with emphysematically distended alveoli and ducts and with more normal tissue. Membranous exudate in several bronchioles, alveolar ducts and alveoli. Haematoxylin and eosin. 26 \times .

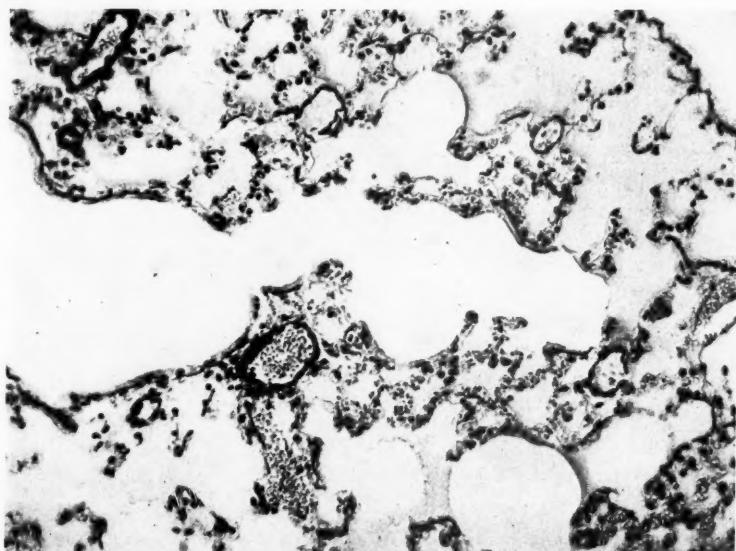


Fig. 3. Bronchiole and alveolar ducts of mouse lung after exposure to oxygen for 5 days covered by hyaline membranes. Most alveoli filled with thin exudate. Capillary stasis. Weigert's elastin stain and haematoxylin-van Gieson stain. 90 \times .

ence of alveolar macrophages and neutrophil leukocytes, and perivascular and peribronchiolar oedema.

In the animals, exposed for 5 and 6 days, the alveoli of considerable parts of the lungs were filled with acidophilic, PAS-positive fluid (Fig. 1). Scattered groups of alveoli exhibited a pneumonia-like picture, the exudate containing numerous white and red blood cells, and alveolar macrophages filled with PAS-positive, acidophilic granules. Small areas of atelectasis were frequently observed (Fig. 2). Eosinophilic, PAS-positive membranes, sometimes 5-10 microns thick, covered a large number of alveoli, alveolar ducts and respiratory bronchioles (Fig. 3). However, even in these animals exposed for 5-6 days, fairly normal pulmonary tissue persisted

in parts of the lungs; at these sites, only capillary stasis could be detected, but no definite changes in the alveolar walls.

Electron Microscopy

The electron-microscopic appearance of the normal mouse lung corresponded in all essentials to that described in the rat and other animals by Low (1952, 1953), Karrer (1956) and others (Fig. 4).

The patchy distribution of the pathologic changes after oxygen exposure was still more pronounced when seen under the electron microscope than under the light microscope (Figs. 5, 8). Apparently normal alveoli persisted even in such lungs in which more than 75 per cent of the volume was heavily consolidated.

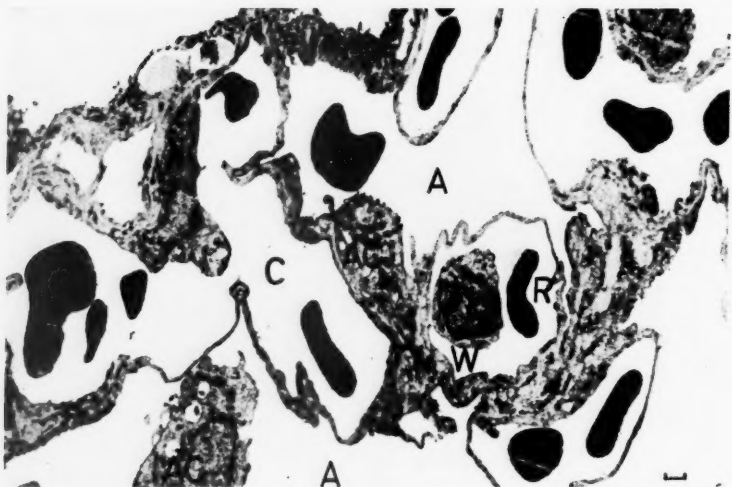


Fig. 4. Survey picture of normal lung tissue in the mouse. In the centre, a white blood cell in a capillary, and in the upper part of the picture a red blood cell in an alveolus. The presence of the latter in the alveolus may be a result of preparation. 3,000 \times .

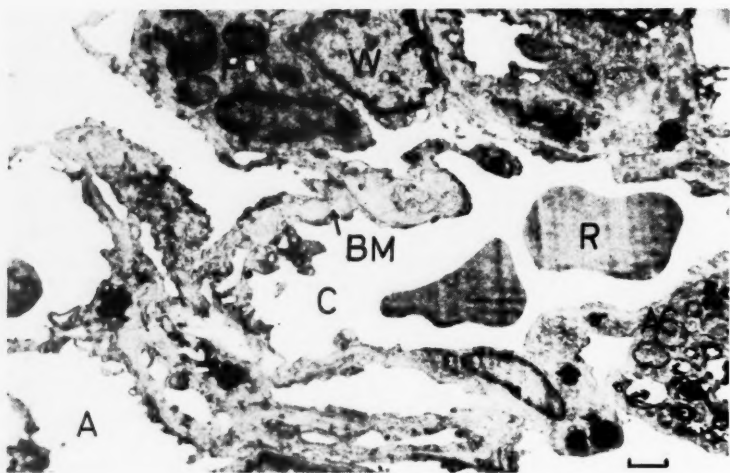


Fig. 5. Survey picture of lung tissue from a mouse exposed to oxygen for 6 days. The alveolar walls are thickened, and patchy changes are present in the basement membrane. In the upper part of the picture are seen two white blood cells, and probably a compressed alveolus. The relatively slight damage is remarkable after such long exposure. 4,500 \times .



Fig. 6. Alveolar region in a mouse lung after exposure to oxygen for 4 days. Three capillaries with two endothelial cell nuclei are visible, as well as typical inclusion bodies. The alveolar epithelial lining appears to be swollen, but a poor embedding result cannot be excluded. 11,500 \times .

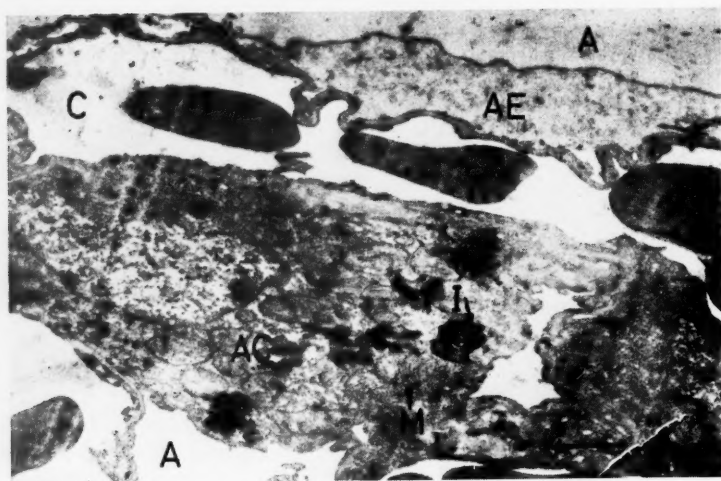


Fig. 7. Pronounced, local alveolar epithelial swelling (AE) in a mouse lung after stay in oxygen for 4 days. 10,000 \times .

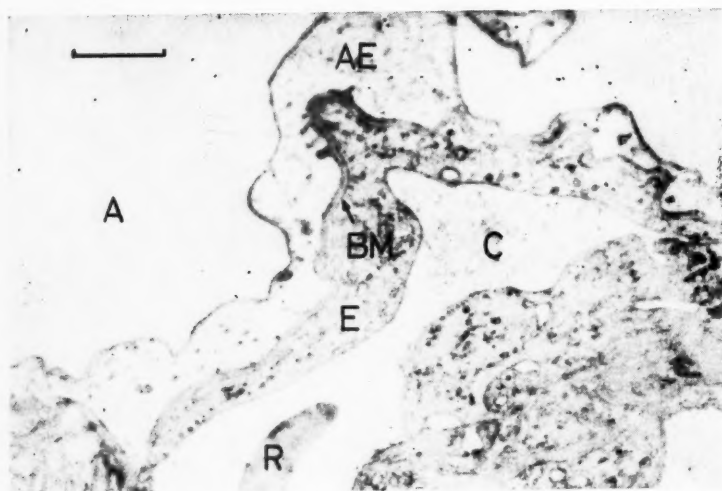


Fig. 8. Alveolar region from a mouse exposed to oxygen for 4 days. Apparent swelling of epithelial and endothelial layers. The basement membrane, at least in the upper part of the picture, has a normal appearance. 13,500 \times .

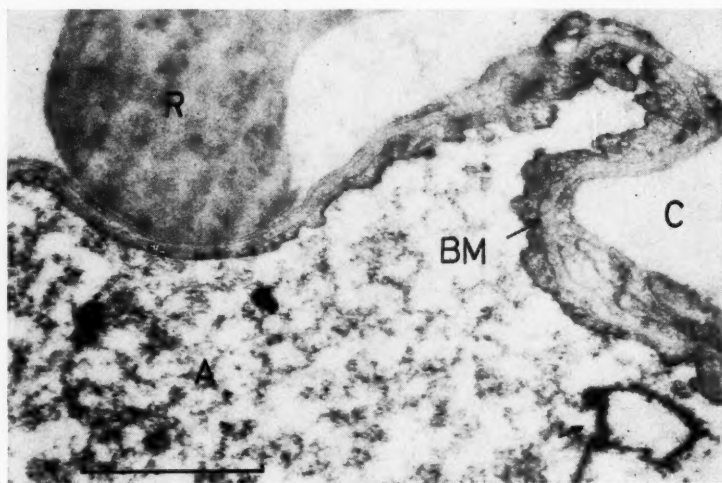


Fig. 9. From alveolus of a mouse exposed to oxygen for 5 days. The alveolus contains a precipitate in which are found threads which might be fibrin. (No unquestionable periodicity is, however, visible. Lower arrow.) 27,000 \times .

In the mice exposed to oxygen for 4 days, scattered groups of alveoli contained a secretion or exudate, which appeared as a granulated precipitate without much contrast. In some alveoli, the thin part of the wall had increased in thickness to about 1–2 microns (Figs. 7, 8, 10). Some agglomeration of blood cells was often seen in the capillaries.

The structure of the lungs after 5 and 6 days' exposure differed in those parts, where atelectasis was present and in the non-atelectatic parts.

In non-atelectatic lung tissue, a large number of alveoli and alveolar ducts, as well as some respiratory bronchioles were filled with exudate of varying appearance. The secretion contained in some alveoli gave little contrast on the electron-microscopic picture, and consisted of a precipitate of fine granules of varying shape and size. Its appearance was similar to that

of the precipitate often formed during fixation of the content of capillaries, although the number of granules might indicate a higher concentration of proteins than in blood plasma. In some alveoli, a denser granular exudate was found. The exudate sometimes contained scattered fibrils, approximately 200–400 Å thick, but no cross-striation could be seen in them (Fig. 9).

Both white and red blood cells were observed in many alveoli.

The alveolar cells varied greatly in structure. Thus, apparently normal cells persisted even in otherwise damaged tissue. In other parts, considerable swelling was visible in the epithelial layer of the alveolar wall. This swelling sometimes appeared as oedema, as judged by the optical density of the cytoplasm. As a rule, the mitochondria in the alveolar cells were completely normal, without swelling or vacuolization, and with normal membrane

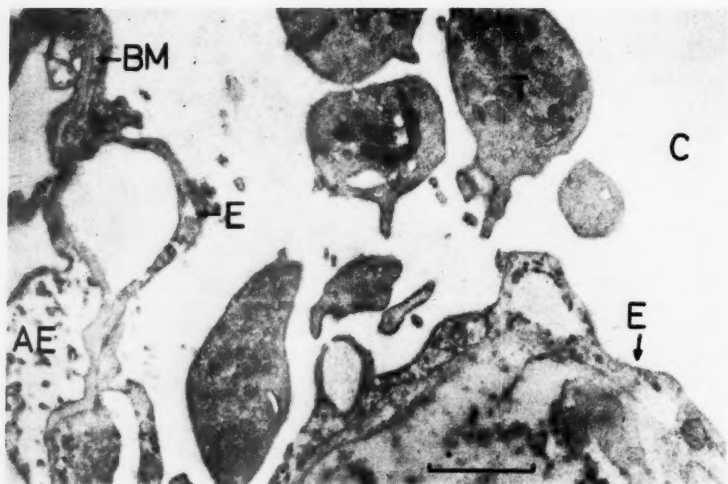


Fig. 10. From alveolus of a mouse exposed to oxygen for 4 days. Apparently severe lesions of the epithelial layer of the alveolar wall, as well as of the endothelial, capillary layer. Large vacuoles are seen in the latter. An interesting feature is the accumulation of thrombocytes close to the destroyed wall. 14,000 \times .

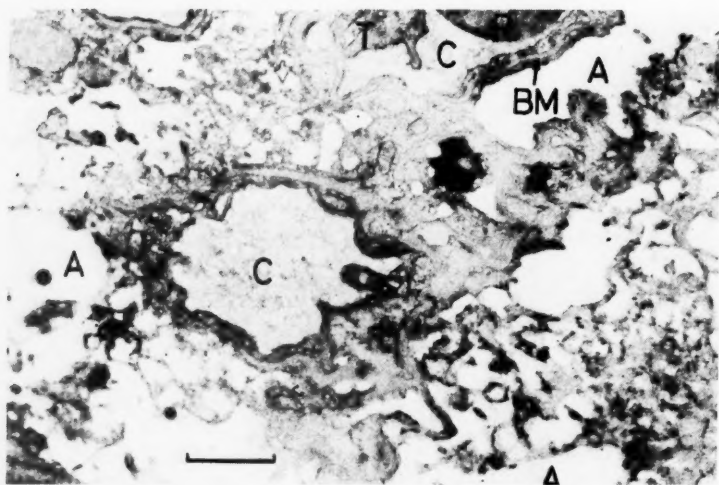


Fig. 11. Partly destroyed alveolar tissue in a mouse lung after exposure to oxygen for 6 days. In the upper capillary, a thrombocyte. The basement membrane and endothelial lining are mostly in surprisingly good condition, whereas degeneration of the epithelial lining is present. 13,000 \times .

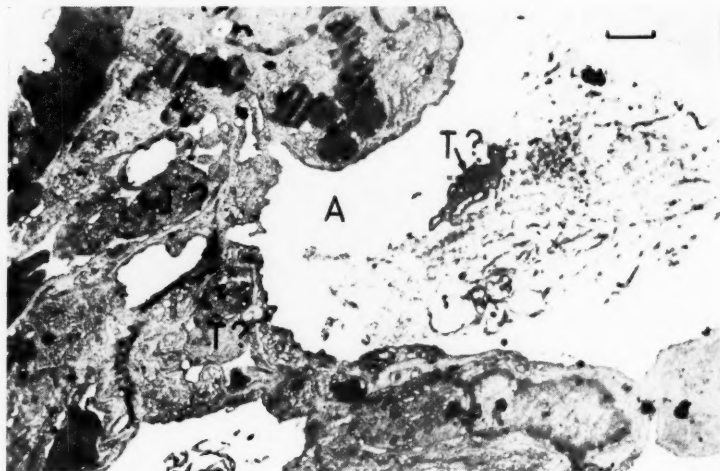


Fig. 12. From alveolar region in the lung of a mouse exposed to oxygen for 6 days. The alveolus in the upper, right-hand part of the picture contains a substance with the appearance of a fibrillar mass, in which a thrombocyte (?) is present. Blood corpuscles, interpreted as thrombocytes, are visible in the capillaries. 6,500 \times .

systems. Typical lamellated bodies were found in the cells, sometimes in large numbers.

Some alveolar cells were attached to the wall only by very thin processes, and other cells lay free in the alveolar lumen. These cells were regarded as alveolar macrophages. Most of them possessed a large number of pseudopodia.

Swelling was observed in endothelial cells as well, although its frequency seemed to be lower. In some endothelial cells, osmophilic granules with a diameter of about 0.5–1 microns, apparently lipid granules, were present. Other cells contained vacuoles of varying size, up to 0.5–1 microns in diameter. Since, however, both granules and a few vacuoles were observed even in normal pulmonary tissue, these formations were not considered to have any unquestionable pathologic signifi-

cance. Similar lipid granules were seen in the alveolar cells (Figs. 6, 12).

The basement membrane between the endothelial and alveolar cells was sometimes slightly swollen and split up, in limited areas, and accumulations of exudate were often found between the basement membrane and the alveolar or endothelial cells (Fig. 10). Alternating with such findings, apparently normal parts of the alveolar wall were visible.

The atelectatic lung tissue was composed of compressed alveoli, with rudimentary air spaces, which were generally filled with exudate of the same type as described above, often mixed with white and red blood cells and more or less disintegrated alveolar cells. The adjacent capillaries were also partly compressed (Figs. 13, 14).

Parts of the alveolar walls in the atelectatic tissue were conspicuously folded and



Fig. 13. Compressed alveolar tissue in a mouse exposed to oxygen for 6 days. Note the folled alveolar wall in the lower part of the picture. The structure of the three layers of the wall is, however, largely normal. $13,000\times$.

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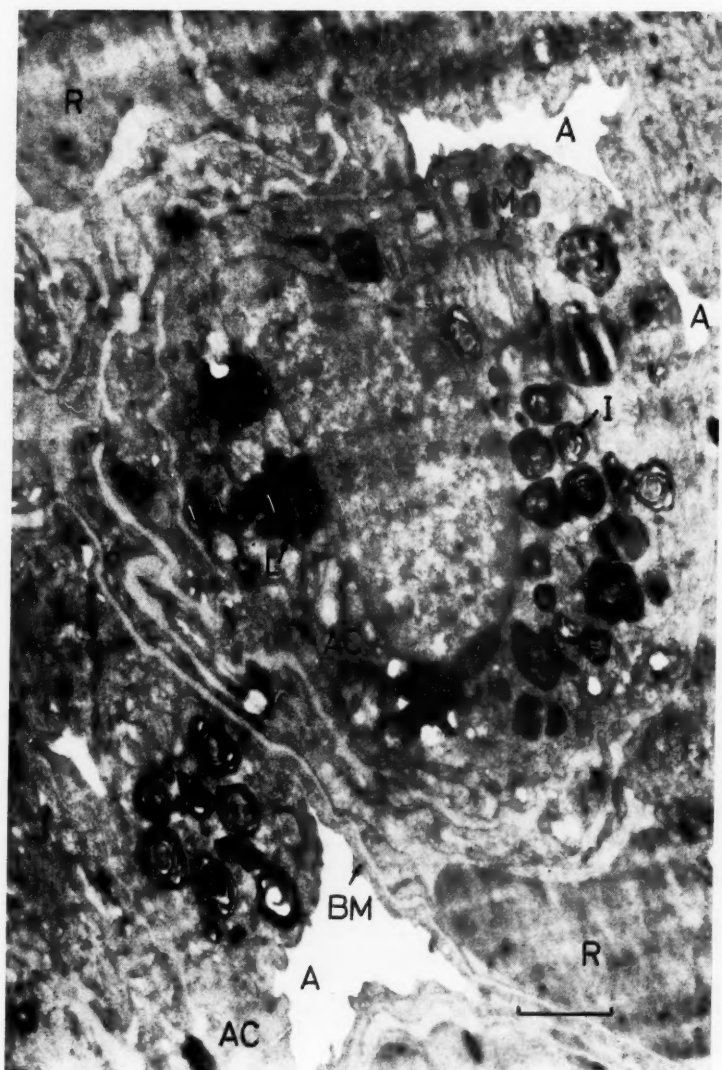


Fig. 14. Alveolar tissue in an atelectatic part of a lung lobe of a mouse exposed to oxygen for 6 days. A remarkable feature is filling of the compressed alveolus by an alveolar cell with mitochondria and typical inclusion bodies. Basement membrane relatively unaltered. 14,000 \times .

the folds densely compressed, forming a 2-3 microns thick, opaque mass in the wall (Fig. 13). In these atelectatic alveoli with folded walls, the nucleus-containing part of the alveolar cell, which normally bulges slightly from the wall into the air space, filled most of the remaining alveolar space. Thus, in these areas, the thickening of the wall between capillary and alveolar lumen was due mainly to folding of the wall.

The width of the capillaries varied greatly in the atelectatic tissue; thus, part of a capillary could be compressed so that the lumen measured only 200-400 Å, whereas other parts were wide and filled with densely packed blood cells.

A striking feature was the presence of numerous thrombocytes in the capillaries of some of the damaged parts.

Bacteriologic Results

The lungs of three of the animals showed no signs of bacteria, as judged by the complete absence of bacterial growth in the cultures. Only a sparse growth of small grey colonies on blood-agar dishes was obtained from the lung homogenates of another three animals. These colonies were not further identified. Another lung homogenate produced a sparse growth of the same grey colonies, together with a few α -haemolytic streptococci.

The type of bacterial growth just mentioned, comprising two kinds of cultures, is regarded as saprophytic. More abundant bacterial growth was found in two animals. In one of them, large numbers of *staphylococcus albus* were present, in addition to sparse growth of the two "saprophytic" types of bacteria. It cannot be ruled out that the former growth was due to con-

tamination. In the second animal with more profuse bacterial growth from the pulmonary homogenate, an abundant growth of α -haemolytic streptococci occurred besides a few colonies of the grey type mentioned earlier. This animal was severely injured by oxygen poisoning, and died spontaneously before preparation. At autopsy, the whole lungs exhibited massive consolidation and congestion. The presence of streptococci may be explained by saprophytic bacteria, descending from the upper respiratory tract during and shortly after death of the mouse.

Thus, despite the fact that the lungs of the animals used for bacteriologic control exhibited severe oxygen damage, two mice dying spontaneously, no consistent bacterial growth was found. Judging by these results it seems highly unlikely that bacteria play any important role in the pathogenesis of oxygen-induced pulmonary disease.

Discussion

The present results support the theory, mentioned in the introduction, that prolonged oxygen exposure causes increased permeability of the alveolar wall, allowing a profuse passage of blood plasma and blood cells. The patchy thickening, which can be observed in the thin part of the wall, might be due either to hypertrophy of the epithelial lining or to accumulation of fluid in the cell. The splitting of the basement membrane and the accumulation of fluid in vacuoles below the alveolar cells, as well as between endothelial cells and basement membrane, seem to constitute another kind of damage to the alveolar wall, permitting increased transport of

fluid from the blood to the alveolar lumen. Even in greatly injured and consolidated parts of the lung, the basement membrane may, however, often be astonishingly well preserved.

Schulz (1956) described a thickening of the alveolar wall and a transport of fluid through it, the fluid appearing in vacuoles. It seems likely that the damage to the alveolar wall described above might allow passage of fluid from the capillary to the alveolar space, thus explaining the presence of exudate in the severely damaged parts of the lung. It is, however, probable that leakage or secretion of fluid from blood to alveolus can occur even when the alveolar wall is fairly normal, as judged by the histologic and electron-microscopic structure. In the light microscope, the passage of white and red blood cells between the endothelial and the alveolar cells, and from capillary lumen to alveolar space, has been demonstrated to be increased in oxygen-poisoned animals. Probably, part of the fluid transport from blood to alveolar air space also takes place between the cells.

The atelectasis does not necessarily involve a change in the alveolar cell, so that the latter forms a cubical epithelium as suggested by Engel (1957) and earlier authors, although a thickening of the thin part of the alveolar wall is sometimes observed. Another mechanism for compression of the alveolus consists of the marked folding of the wall, with close packing together of the sharp folds. Seen in the light microscope at low numerical aperture such packing together of many, small folds may be interpreted as thickening of the alveolar cells forming a cubical epithelium.

The vacuolization of the mitochondria in the alveolar cells, as described by Schulz, is not a characteristic lesion of the oxygen-intoxicated lung, but may perhaps be regarded as a sign of cellular degeneration in those parts of the lung where severe damage to the alveolar wall has been produced. Such swelling and vacuolization is sometimes observed in the free macrophages, lying in the spaces of the alveoli. In this connexion, it is necessary to stress the difficulties of ensuring a reliable fixing and embedding technique. In view of these difficulties, any pathologic changes observed under the electron microscope must be interpreted with the utmost caution.

The alveolar membranes seem to include thickened alveolar cells, coagulated exudate, which is probably derived from the blood, and remains of degenerated alveolar cells and blood cells. Whether or not this exudate contains fibrin could not be definitely established by the present investigation. It is true that fibrils sometimes appeared in the exudate but no definite cross-striation could be observed in them. Fibrin has, in fact, been demonstrated in hyaline membranes, by means of fluorescein-labelled antibodies (Gitlin & Craig 1956). However, this fibrin is generally not amenable to staining with ordinary fibrin-staining procedures (Berfenstam *et al.* 1958), and it has been argued that fibrin in hyaline membranes occurs in an anomalous form. It is possible that the non-striated fibrils observed in the present investigation represent such anomalous fibrin.

Summary

1. Acidophilic, periodic-acid-Schiff positive membranes in the alveoli, alveolar

ducts and respiratory bronchioles, as well as atelectasis and pulmonary exudation, were produced in adult mice by means of oxygen exposure for 4-6 days. The disease resembled human neonatal "hyaline membrane disease".

2. Electron-microscopic studies of the damaged pulmonary tissue showed great variation, apparently normal alveolar walls alternating with damaged ones, even in alveoli with membranes, atelectasis and exudate. Scattered injuries to the alveolar walls consisted of swelling of the walls, fragmentation of the basement membrane between alveolar and endothelial cell layers, and accumulation of exudate between the basement membrane and the alveolar or endothelial cell. Atelectatic alveoli often possessed apparently normal alveolar layers without any appreciable thickening of the separate layers. Thickening of the whole wall was due, at least in part, to marked, sharp folds in the basement membrane and adjacent parts of alveolar and endothelial cells.

3. Bacteriologic cultures of homogenized pulmonary tissue, which had been severely damaged by oxygen exposure for 5 days, did not yield any characteristic bacterial growth.

4. It is concluded that prolonged stay in concentrated oxygen causes alveolar damage, probably by increasing the transport of blood proteins and blood cells *through* as well as *between* the endothelial and alveolar cells.

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Abbreviations

A = Alveolus, AC = Alveolar Cell, AE = Alveolar Epithelium, BM = Basement Membrane, C = Capillary, EC = Endothelial Cell, E = Endothelium, I = Inclusion Body, L = Lipoid Granule, M = Mitochondrion, P = Polynuclear White Blood Cell, R = Red Blood Cell, T = Thrombocyte (Platelet), W = White Blood Cell (not further specified).

The scale lines in the figures represent a length of 1 micron.

Lésions pulmonaires consécutives à une intoxication par l'oxygène. Etude réalisée sur des souris à l'aide du microscope électronique.

L'apparition de membranes acidophiles positives à l'épreuve de la réaction de Schiff dans les alvéoles, les canaux alvéolaires et les bronchioles respiratoires ainsi que celle d'atélectasies et d'exsudats pulmonaires ont été provoquées chez des souris adultes en les exposant aux effets de l'oxygène durant 4 à 6 jours. Les altérations obtenues furent semblables à celles que l'on observe en médecine humaine dans la maladie de la membrane hyaline chez les nouveau-nés. L'examen des tissus pulmonaires lésés au microscope électronique donna des résultats très

variables en ce sens que des parois alvéolaires apparemment normales alternaient avec des parois endommagées, même dans les alvéoles présentant des membranes, des atélectasies et des exsudats. Ces altérations éparses des parois alvéolaires consistaient en gonflements des parois, en fragmentations de la membrane basale entre les couches cellulaires alvéolaire et endothéliale, et en accumulations d'exsudats entre la membrane basale et les cellules alvéolaires ou endothéliales. Les alvéoles atteints d'atélectasie présentaient souvent des couches alvéolaires apparemment normales sans épaississement appréciable des différentes couches. L'épaissement de toute la paroi était dû, tout au moins

en partie, à des plissements marqués et profonds dans la membrane basale ainsi que dans les portions adjacentes des couches cellulaires alvéolaire et endothéliale. Les cultures bactériologiques de tissus pulmonaires homogénéisés, qui avaient été sévèrement endommagés à la suite d'une exposition aux effets de l'oxygène durant cinq jours, ne firent apparaître aucune prolifération bactérienne caractéristique. On en conclut qu'un séjour prolongé dans une atmosphère à forte concentration en oxygène provoque l'apparition de lésions alvéolaires et que celles-ci sont probablement la conséquence d'une augmentation des quantités de protéines sanguines et de globules sanguins transportées à travers ainsi qu'entre les cellules endothéliales et les cellules alvéolaires.

Lungenschädigung durch Sauerstoffvergiftung. Elektronenmikroskopische Studie bei Mäusen.

Acidophile, auf Schiff's Reaktion positive Membranen in den Alveolen, den Alveolen- gängen und Bronchiolen, sowie Atelektase und Lungenexsudat wurden bei der Einwirkung von Sauerstoff durch 4-6 Tage ausgesetzten Mäusen hervorgerufen. Die Erkrankung ähnelte der menschlichen „hyalinen Membrankrankheit“ bei Neugeborenen. Elektronen-mikroskopische Studien der geschädigten Lungengewebe wiesen grosse Mannigfaltigkeit auf, nämlich eine Abwechslung von anscheinend normalen mit geschädigten Alveolenwänden sogar in Alveolen, die Membranen, Atelektase und Exsudat aufwiesen. Die zerstreuten Schädigungen der Alveolenwände bestanden aus Schwellung der Wände, Fragmentierung der Basalmembran zwischen den alveolären und endothelialen Zellenlagern und Ansammlung von Exsudat zwischen der Basalmembran einer- und den Alveolen- oder Endothelzellen andererseits. Atelektatische Alveolen besaßen oft anscheinend normale alveoläre Zellenlager ohne merkliche Verdickung der besonderen Schichten. Verdickung der ganzen Wand war zumindest teilweise auffallenden, scharfen Falten der Basalmembran und der anliegenden Teile der Alveolen- und Endothelzellenlager zuzuschreiben. Kul-

turen mit homogenisiertem Lungengewebe, welches durch 5 Tage lange Sauerstoffaussetzung geschädigt worden war, ergaben kein charakteristisches Bakterienwachstum. Es wird daraus geschlossen, dass langes Verbleiben in konzentriertem Sauerstoff die Alveolen wahrscheinlich dadurch schädigt, dass der Transport von Blutproteinen und Blutzellen durch die als auch zwischen den Alveolen- und Endothelzellen vergrößert werde.

Alteraciones pulmonares provocadas por la intoxicación por oxígeno. Estudio con el microscopio electrónico en ratones

Mediante la exposición al oxígeno durante 4-6 días se produjeron en ratones adultos membranas acidófilas, Schiff positivas, en los alvéolos, conductos alveolares y bronquiolos respiratorios, así como atelectasias y exudación pulmonar. El proceso semejaba la «enfermedad de la membrana hialina» humana neonatal. Los estudios con el microscopio electrónico del tejido pulmonar lesionado mostraron gran variación: aparentemente paredes alveolares normales alternaban con otras alteradas, incluso en los alvéolos con membranas, atelectasia y exudado. Las lesiones diseminadas de las paredes alveolares consistían en tumefacción de la pared, fragmentación de la membrana basal entre las células alveolares y endoteliales, y acúmulo de exudado entre la membrana basal y la célula alveolar o endotelial. Los alvéolos atelectásicos poseían las distintas capas parietales aparentemente normales, sin ningún engrosamiento apreciable. El engrosamiento de la pared se debía, por lo menos en parte, a repliegues muy marcados de la membrana basal y porciones adyacentes de las células alveolares y endoteliales. Los cultivos bacteriológicos de los tejidos pulmonares homogeneizados, que habían sido gravemente lesionados por la exposición al oxígeno durante 5 días, fueron negativos. Se concluye que la permanencia prolongada en oxígeno concentrado provoca alteraciones alveolares, probablemente por aumentar el transporte de proteínas hemáticas y células sanguíneas tanto a través como entre las células endoteliales y alveolares.

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From the Departments of Paediatrics, Centrallasarettet, Boden (Head H. Enell) and Centrallasarettet, Skellefteå (Head L. Söderhjelm)

Intramuscular Iron as Anaemia Prophylaxis in Premature Infants

by RAGNHILD HILLBORG and LARS R. NILSSON

Anaemia in premature infants may appear at various ages. The early anaemia, which reaches its maximum at the age of 8-12 weeks, is due to several factors and is influenced only to a small degree by iron therapy (3, 16, 18).

The late anaemia may appear as a continuation of the early anaemia, but mostly it appears during the second half-year of life (10). It is caused mainly by iron deficiency. The amount of iron at the time of birth is in direct proportion to the birth weight (23) and is found mainly in the circulating blood. For this reason premature infants have less iron in the body at birth than full-term infants. The need of iron is however great because of the rapid growth. The amount of iron that can be resorbed from the food is insufficient in the case of many premature infants, who thus develop a more or less marked iron deficiency anaemia.

Iron is generally administered to premature infants as a matter of routine in order to prevent late anaemia. One generally gives peroral iron for several months from the age of 1-2 months. It is sometimes difficult to carry through the treat-

ment because of its long duration and intolerance troubles such as nausea, emesis, diarrhea or obstipation. The endurance of the mother is another factor that may jeopardize the treatment.

In 1955, Gaisford & Jennison reported good preliminary results of intramuscular iron treatment as anaemia prophylaxis to premature infants. The following is a report of an investigation aiming at ascertaining the value of such prophylaxis.

Materials and Methods

The material comprises infants with a birth weight lower than 2200 g treated at the Paediatric Departments of Boden and Skellefteå during the latter part of 1955 and the entire year 1956 because of prematurity or low weight caused by multiparity. Twenty-nine infants were treated with intramuscular iron, and 28 infants were control cases. None of these infants have had hemolytic or hyporegeneratory anaemia.

The birth weight in the group treated with intramuscular iron varied between 1020 and 2100 g, and in the control group between 1440 and 2190 g. The former group is somewhat overrepresented as to low-weight infants (5 below 1400 g), but for the rest the distribution is even. The two groups are considered equivalent on the whole. Thir-

ty-one of the children are boys and 26 girls. Six pairs of twins (binovular), 2 single twins and one set of triplets are found in the series.

Seip a.o. has made the observation that the last-born in a pair of twins frequently has higher haemoglobin concentration at birth than the first-born. In 4 pairs of twins in this material the last-born has higher birth weight, but only in 2 pairs higher haemoglobin concentration. It is thus of no essential importance how the twins are distributed between the treatment and the control group.

The infants were cared at the Paediatric Department from the first day of their life with the exception of one pair of twins, who were sent over from elsewhere in the course of the first week. The lying-in time varied between 3 weeks and 4 months. During their first time the infants were fed with breast milk, later on with addition of ordinary or acidified half-gruel. AD-vitamins were given from one month of age, fruit juices from 3 months, and pulps from 4 months. After the discharge from the Hospital the infants were controlled at the Children's Welfare Centres or ambulatorily at the Hospitals.

The blood values were determined in the course of the first 24 hours and after that once a week during the period of hospital care. The haemoglobin concentration was determined with Ljungbergs colorimeter (100 % haemoglobin = 16.0 g%). After the discharge the majority of the infants were checked twice a month up to the age of 3 months, once a month to 6 months and after that every second month up to the age of one year. Some cases could not be checked so often because of great distances.

Imferon^R (produced in Sweden by Pharmacia under licens of Benger Ltd, England) was used for the injections. Imferon is a solution of an iron-dextran complex containing 50 mg iron per ml. Its pharmacology has been investigated by Martin *et al.*

Deep intramuscular injections were given during the third week of life. By displacing the skin before the injection, the puncture canal got an angular course after the injection,

which lessens the risk of discolouring around the place of injection. As a rule, 150 mg iron (3 ml) were given in daily doses of 25 mg ($\frac{1}{2}$ ml). Two hundred mg were given to two infants, 125 mg to two and 100 mg to three infants. The control infants were given iron perorally in daily doses of 20–30 mg bivalent iron (ferrosi pyrophosphas-*Guttafer*^R) for 2–4 months. The treatment was started when the haemoglobin concentration had gone down to about 11.0 g%, which occurred at the age of 6–8 weeks. Seven infants had no need of extra iron supply, 3 infants got no iron for other reasons.

One of the infants died at the age of nine months from fulminant bronchopneumonia. Three infants showed symptoms of brain damage. For the rest, the general condition and weight increase of the infants were satisfactory.

Results

The mean haemoglobin concentration at various ages and its average change in the groups are recorded in Tables 1 and 2. The considerable variation between individuals receiving the same treatment appears from Table 3.

The initial decrease of the haemoglobin concentration is stopped earlier in the group receiving intramuscular iron than in the control group, and the subsequent increase of the values also starts earlier. The difference between the two groups as to the change of haemoglobin concentration during the period of 8–12 weeks of age is significant at the 5 % level.

From the age of 10 weeks the infants in the injection group have a higher average haemoglobin concentration than the infants in the control group. Thus, at the age of 6 months the haemoglobin level was lower than 11 g% in 4 out of 25 infants in the former group and in 12 out of 25 infants in the latter group, and this

TABLE 1. *Mean haemoglobin concentration (g %) at various ages. The figures in italics indicate the number of measurements on which each mean is based.*

	0 w.	2 w.	8 w.	10 w.	12 w.	4 m.	6 m.	8 m.	12 m.
Imferon group	19.2	17.5	10.9	10.9	11.5	12.3	12.3	12.3	12.3
29 children	<i>28</i>	<i>29</i>	<i>24</i>	<i>23</i>	<i>20</i>	<i>24</i>	<i>25</i>	<i>23</i>	<i>23</i>
Control group	20.1	18.1	11.2	10.6	10.6	11.4	11.4	11.4	11.6
28 children	<i>26</i>	<i>27</i>	<i>21</i>	<i>14</i>	<i>20</i>	<i>24</i>	<i>25</i>	<i>20</i>	<i>22</i>

TABLE 2. *Mean change in haemoglobin concentration (g %) over selected periods for infants examined at the beginning as well as at the end of the period.*

	0 w.-8 w.	8 w.-12 w.	12 w.-4 m.	4 m.-12 m.
Imferon group	- 8.3	+ 0.72	+ 0.85	- 0.15
	<i>23</i>	<i>18</i>	<i>19</i>	<i>21</i>
Control group	- 8.9	- 0.54	+ 0.62	+ 0.34
	<i>21</i>	<i>14</i>	<i>19</i>	<i>19</i>

TABLE 3. *Standard deviation of individual changes of haemoglobin concentration within treatment groups. Only infants examined at the beginning as well as at the end of the period are included.*

0 w.-8 w.	8 w.-12 w.	12 w.-4 m.	4 m.-12 m.
2.0	1.4	1.1	1.55

The statistical calculations were performed by E. Leander, Department of Statistics, University of Stockholm.

difference is also significant at the 5 % level.

Complications from the treatment were noticed in one case, who got transient discolouring around the place of injection. There were no infiltrations, no reddening of the skin, and no general reactions.

Earlier experience of ferridextranate in treatment of manifest iron deficiency anemia in children has been good (1, 9, 13, 20, 21, 22). No complications have been re-

ported beyond local discolouring of the skin in single cases. Adult patients however, have shown general reactions in individual cases, probably mostly of an allergic nature (2).

Discussion

The result of the investigation shows that the haemoglobin level in the infants treated parenterally with iron is significantly higher than that of the control infants during the period of 8-12 weeks of age. A significantly higher haemoglobin concentration is also found in the imferon group at the age of 6 months.

The two groups contain a category of mostly somewhat larger premature infants, who have satisfactory blood values without extra iron supply. These infants were not treated in the control group, but they were treated in the treatment group, from which they could not be separated beforehand. This difference may of course be re-

flected in the blood values, but probably not to any considerable extent.

The time of starting the iron treatment is different in the two groups. Earlier peroral iron supply may possibly have caused somewhat earlier increase of the mean haemoglobin concentration in the control group (3). This causes a certain doubtfulness in judging the result, but from a practical point of view it is unimportant.

When starting this investigation we planned to allot strictly every second premature infant in order of birth to the imferon group and the others to the control group. If this plan had been followed, the conclusion would have been, that the better increase of the haemoglobin concentration in the group treated with imferon really was a result of this treatment. But as a matter of fact, the initial plan has not been followed strictly. There has been room for a subjective element in the allotment. The data, however, indicate that there is a predominance of infants with relatively low birth weight and low haemoglobin concentration in the imferon group. It is therefore reasonable to conclude that our results are indicative of a real treatment difference.

The marked increase of the haemoglobin concentration commencing already at the age of 10 weeks in the infants that have been given imferon cannot be a nonspecific stimulus effect from the injections given much earlier, but it is interpreted as indicating that many premature infants have iron deficiency very early. Seip & Halvorsen have observed that haemosiderin may disappear from the bone marrow already at the age of 6-8 weeks in small premature infants. Smith *et al.*, on the other

hand, have found that full-term infants have no need of exogenous iron supply before the age of 3-4 months.

The iron requirement during the first year varies rather considerably from one individual to another. This has been elucidated among others by Sturgeon, who has calculated, by aid of varying normal values for haemoglobin and blood volume and varying rate of growth, that the iron requirement of full-term infants during the first year of life may vary between 106 and 285 mg. Josephs has calculated that about 33 mg iron are required for each kg of growth with an estimated blood volume increase of 76 ml. On an exclusive milk diet, about 6 mg iron per month can be absorbed from the food (8), but on a diet that is richer in iron the absorption increases considerably, especially in cases of iron deficiency (15). It is thus difficult to define precisely how much iron should be given to premature infants beyond what is absorbed from the food. We have estimated the requirement of the smallest premature infants to be 200-250 mg iron, and that of the larger premature infants to be 100-150 mg. Part of the iron-dextran complex is absorbed but slowly from the intramuscular depot (5, 6, 14), but this is no drawback in this connection and has not influenced the calculation of the dose of imferon.

Summary

Twenty-nine premature infants with a birth weight between 1020 and 2190 g were given 100-200 mg iron in the form of intramuscular injections of ferridextranate (Imferon^R) during the third week of life as anemia prophylaxis. In a control

group of 28 infants, 18 were treated with iron perorally for a couple of months after their haemoglobin concentration had decreased below 11,0%. Seven out of the remaining 10 infants needed no extra iron supply, as their blood values were satisfactory.

The haemoglobin concentration increased significantly earlier in the group of infants treated with iron parenterally,

and from the age of 10 weeks for the remaining part of the first year of life it was higher than in the control group. At the age of one year the mean haemoglobin concentration was 12,3 g % in the imferon-group and 11,6 g % in the control group. The treatment was simple and brought no other complications than transient local discolouring in one case.

Traitement préventif de l'anémie chez les nourrissons prématurés par l'administration de fer en injections intramusculaires

Vingt-neuf bébés prématurés qui, à la naissance, pesaient entre 1020 et 2190 grammes, ont reçu, durant la troisième semaine de leur vie, 100 à 200 mg de fer sous forme d'injections intramusculaires de dextranate ferrique (Imferon[®]) à titre de médication préventive contre l'anémie. Dans un groupe de contrôle composé de 28 bébés, 18 furent traités par l'administration perorale de fer durant quelques mois après que leur taux d'hémoglobine soit tombé en dessous de 11,0 g %. Sur les 10 enfants restants, il y en eut sept chez lesquels la formule sanguine resta satisfaisante et pour lesquels il ne fallut pas avoir recours à l'administration de suppléments de fer. L'augmentation du taux d'hémoglobine fut nettement plus précoce chez les nourrissons qui avaient reçu le fer par voie parentérale et à partir de la dixième semaine jusqu'à la fin de la première année, le taux d'hémoglobine fut plus élevé chez ces enfants que chez ceux du groupe de contrôle. A l'âge d'un an, le taux moyen d'hémoglobine s'élevait à 12,3 g % chez les enfants traités à l'Imferon et à 11,6 g % chez les enfants du groupe de contrôle. Le traitement fut simple à appliquer et, à part une décoloration locale passagère dans un cas, aucune complication n'a été observée.

Intramuskuläre Verabreichung von Eisen als Anämieprophylaxe bei vorzeitigen Kindern.

Neunundzwanzig Frühgeborenen mit einem Geburtsgewicht zwischen 1020 und 2190 g erhielten 100-200 mg Eisen in der Form von intramuskulären Injektionen von Ferridextranat (Imferon[®]) während der dritten Lebenswoche als Prophylaxis gegen Anämie. Aus einer Kontrollgruppe von 28 Kindern wurden 18 mit peroral verabreichtem Eisen durch 2 Monate behandelt, nachdem ihre Hämoglobinkonzentra-

tion unter 11 g % gefallen war. Sieben von den restlichen 10 Kindern brauchten keine zusätzliche Eisenzufuhr, da die Blutwerte bei ihnen zufriedenstellend waren. Die Hämoglobinkonzentration stieg bei der Gruppe der mit parenteral zugeführtem Eisen behandelten Kindern bedeutend früher an und vom Alter von 10 Wochen bis zum Ende des ersten Lebensjahres war sie höher als bei der Kontrollgruppe. Im Alter von einem Jahr betrug die mittlere Hämoglobinkonzentration 12,3 g % bei der Imferongruppe und 11,6 g % bei der Kontrollgruppe. Die Behandlung war einfach und brachte ausser einer vorübergehenden örtlichen Verfärbung in einem Falle, keine anderen Komplikationen mit sich.

Hierro intramuscular como profilaxis de la anemia en niños prematuros

Veintinueve niños prematuros con un peso al nacer entre 1020 y 2190 gr. fueron tratados con 100-200 mg. de hierro en forma de inyecciones intramusculares de ferridextranato (Imferon[®]) durante la tercera semana de vida como profilaxis de la anemia. En un grupo testigo de 28 niños, 18 fueron tratados con hierro por vía peroral durante un par de meses después que su concentración de hemoglobina había disminuido por debajo de 11,0 g %. Siete de los 10 niños restantes no requirieron ulteriores complementos de hierro, pues su cuadro hemático era satisfactorio.

La concentración de hemoglobina aumenta significativamente más pronto en el grupo tratado con hierro por vía parenteral, y desde la edad de 10 semanas al resto del primer año de vida fué mas elevada que en el grupo testigo. A la edad de un año la concentración media de hemoglobina era de 12,3 gr % en el grupo tratado con Imferon y de 11,6 gr % en el testigo. El tratamiento es simple y no adujo otras complicaciones que despigmentación local transitoria en un caso.

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(R. H.)
Sollentuna
Sweden

CASE REPORT

Decreased Bone Marrow Function in Hemolytic Disease of Newborn

Report of a Case with Severe Anemia and Prolonged Persistence of Antibodies

by BERTIL LINDQUIST and LARS RYTTER

From the Pediatric Clinic, University of Gothenburg, and the Blood Bank, Sahlgren's Hospital, Gothenburg, Sweden.

Although hemolytic disease of the newborn on the whole shows a uniform picture, cases with more or less atypical features from both clinical and serologic points of view are also seen. In some cases an anemia develops at an interval of 3–4 weeks after birth. This is usually the result of the normal decay of donor red cells and failure of survival of newly formed infants red cells. In the following a case of severe anemia is reported, which was apparently due to a decrease in bone marrow function. The pathogenesis of this is discussed.

Case Report

MOTHER.—At the birth of the third child she was 30 years old. She had always been healthy except for some infections of the upper respiratory tract, and had never received any blood transfusion. Apart from her incompatibility disorder all her three pregnancies had been normal; the last child was delivered by caesarean section. During the *first pregnancy* no close examination of her blood groups was performed. During the *second pregnancy* her blood groups were determined to A Rh(–). The blood groups of her husband were found to be A Rh(+),

with subgroups Rh₁ Rh₂. About one month before delivery there were signs of Rh-immunization in her serum in the presence of antibodies of the anti-D type with the following titres: albumin 64, trypsin 64 and papain 128. During the *third pregnancy* the antibodies of the mother were examined at repeated intervals before delivery (Table 1). Towards the end of the pregnancy there was a marked rise in the titres of the antibodies. The mother was delivered by caesarean section about 1 month before term.

TABLE 1. *The Rh antibody titres of the mother during her third pregnancy, and of the child (umbilical cord blood).*

Interval before delivery (months)	Antibodies examined against		
	Ordinary red cells (in albumin)	Trypsin-treated red cells	Papain-treated red cells
5	32	128	256
3	64	156	512
1½	32	512	1,024
½	8000	16,000	32,000
0	2048 ^a	50,000	50,000
Umbilical cord	512	4,096	16,000

^a "Prozone phenomenon".

TABLE 2. Hematologic laboratory findings in the child during the first hospital admission.

Age (days)	Hemoglobin (percentage)	Red cells (millions/mm ³)	White cells (thousands/mm ³)	Bilirubin (mg per 100 ml)	Remarks
0 (cord blood)	49	1.9	9.4		Exchange transf.
$\frac{1}{2}$	106	5.0	33.0	6.8	
1	78	3.2		25.2	Exchange transf.
2	75	3.6		24.4	Exchange transf.
4	95	4.0	16.0	9.8	
10	72	3.8		1.3	
20	62	3.1	9.2	0.5	Discharge

CHILDREN.—The mother has born 3 girls of which two were alive at birth. The *first child*, born seven years earlier, is still alive and healthy, and there were no signs of hemolytic disease at birth (birth weight 3100 g). Six years later the *second child* was born, and she was stillborn. She was a full-term infant with a birth weight of 3510 g and a length of 54 cm, but macerated. The blood groups of this child were A Rh(+). The direct Coombs' test was positive.

The *third child* had a birth weight of 2400 g. She was pale with a yellow colour of the skin at birth, but her general condition was fairly good. Physical examination of the heart and lungs revealed nothing pathological. There was moderate hepatosplenomegaly. In the cord blood antibodies against the D-factor were found with the following titres: albumin 512, trypsin 4096 and papain 16,000 (Table 1). The ABO group was determined as A, and the red cells tested against complete anti-D-serum were found to react Rh(-) due to "blocking" or "complete coating" by maternal anti-D-antibodies. A Coombs' test performed directly on the red cells of the patient was, however, positive. Examination of umbilical cord blood revealed a marked anemia with a hemoglobin of 49 per cent¹ and a red cell count of 1.9 millions (Table 2). The differential count was essentially normal and in the blood film 7 nucleated red cells were observed per 100 white cells, the white cell count being 9400 per mm³.

¹ 100 per cent equal to 13.8 g.

A *first* exchange transfusion of about 400 ml Rh(-) blood was carried out about 1 hour after birth. Towards the end of the transfusion the patient had a cyanotic attack, and on this account the transfusion was interrupted. Three hours later the bilirubin value was 6.8 mg/100 ml, and after a further 16 hours a value of 25.2 mg/100 ml was noted. The blood film now contained 45 nucleated red cells per 100 white cells. A *second* exchange transfusion of about 400 ml blood was performed without complications. The following day the value of the serum bilirubin was practically unchanged, and a *third* exchange transfusion of about 500 ml blood was carried out without any side reactions. Two days later a marked decrease of the serum bilirubin to a value of 9.8 mg per 100 ml was noted. During these few days after birth the values of the hemoglobin and red cells only showed smaller variations with a definite increase of the values immediately after the transfusion (Table 2).

Over the following days there was a gradual decrease of the values of the hemoglobin and red cells to about 60 per cent and 3.0 millions, respectively, on discharge. The child was then said to be in a good condition. There was, however, a progressive development of an anemia, and therefore the child again was admitted to the Clinic.

On admission the *second time* she was 1½ months old and weighed 3400 g. She was very pale but otherwise her general health was good. Physical examination of the heart, lungs and abdomen showed no signs of a

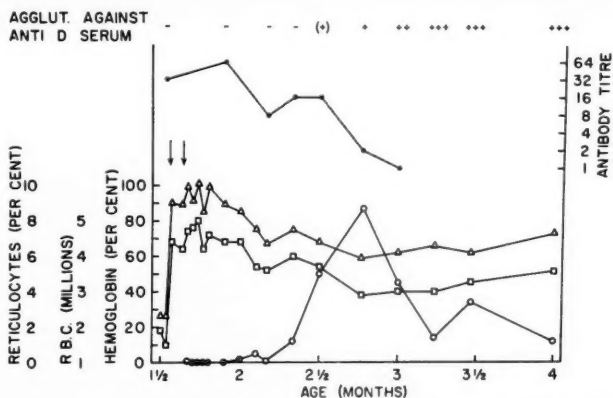


Fig. 1. Hematologic and serologic findings of the child during the second hospital admission. Arrows indicate blood transfusions. Symbols: Δ , Hemoglobin, per cent (100 per cent = 13.8 g); \square , red blood cells, millions per mm³; \circ , reticulocytes, per cent; \bullet , antibody titre.

pathological condition. The lymph nodes were not palpable. X-rays of the skeleton and lungs were normal. She had a marked anemia with a hemoglobin percentage of 26 and a red cell count of 1.9 millions. The white cell count was 7000 per mm³ with a normal differential count, the bilirubin value was normal on repeated determinations.

The patient was now given 2 transfusions of Rh(-) blood, one consisting of 100 ml of ordinary blood, and another consisting of 40 ml of a concentrated red cell suspension, i.e. together a little less than the calculated need. As expected there was a rise of the hemoglobin percentage and red cell count to normal values, but no reticulocytes could, however, be observed (Fig. 1). On a new examination of the Rh system at the second admission—after the transfusions were given—the blood of the patient was found to contain only Rh(-) cells. The direct Coombs' test was negative. In the serum antibodies were demonstrated in a titer of 32 when reactions were carried out against enzyme-treated red blood cells. A *bone marrow biopsy specimen* showed a somewhat scanty occurrence of the different cells. There were signs of decreased erythropoiesis but of a normoblastic type without megaloblasts. No anisopoikilocytosis was observed, nor was

there any polychromatophilia. Lymphopoiesis was somewhat increased but of a normal type, and myelopoiesis was somewhat decreased.

Following this there was a moderate drop of the hemoglobin and red cell values (Fig. 1), and when these, about three weeks after admission, had decreased to 75 per cent and 4.5 millions, respectively, reticulocytes were for the first time observed in the blood film—a value of 1.2 per cent was noted (Fig. 1). A *bone marrow biopsy specimen* still showed signs of somewhat decreased erythropoiesis but of a normoblastic type. Lymphopoiesis was essentially normal, but in myelopoiesis a slight increase of immature myeloblastic cells was observed, which showed a negative peroxidase reaction. Antibodies were still found in her serum, however, with a decreasing titre (Fig. 1).

When the girl was 2 3/4 months old a definite reaction of some of the red cells against anti-D-serum was for the first time demonstrated (type R₂), and now it was also possible to obtain a positive Coombs' test after coating the child's blood cells with strong univalent Rh-antibodies. About 2 weeks later her blood was definitely free from red cells of type Rh(-), and at the same time no more antibodies could be demonstrated in the serum.

The hemoglobin and the red cell values had stabilized to about 65 per cent and 3.3 millions respectively, and the reticulocyte count, which now was 2.2 per cent, had during the preceding weeks shown a peak of 8.7 per cent.

RECAPITULATION.—The clinical picture of the disease of the child during her first stay at the clinic did not differ from what was to be expected with respect to the incompatibility observed. A divergent development was first recognized when at the age of 6 weeks she was admitted to the Clinic, for the second time. A severe anemia was now observed. Although the child probably was Rh(+), it was now and during the next month impossible to demonstrate any red cells from the child's own erythropoiesis in the peripheral circulation. During the same time, however, free antibodies were demonstrated, although in a low concentration as compared to the initial values. A definite disappearance of the antibodies was not observed until the child was 2½ month of age, and at about the same time Rh(+) red cells at first appeared in the peripheral circulation. A definite increase of the reticulocytes was now also found; the peak was, however, not reached until the antibodies had completely disappeared from the serum of the child.

Discussion

In spite of the high antibody titre of the mother as well as of the child (Table 1), and although the mother had previously given birth to a stillborn child, the initial course of the disease was of no greater severity than that usually seen in incompatibility of a moderate degree. This might possibly be explained by the presence of a so-called third antibody, which is said to prevent agglutination of other antibodies (Levine, 1946; Mohn & Witebsky, 1948)—cf. the "prozone phenomenon" observed in the serum of the mother at delivery.

In incompatible children of Rh-iso-

immunized mothers antibodies are usually demonstrated only within an interval of 1–2 weeks after birth (when exchange transfusions have been performed). An adsorption of the antibodies to the red cells of the child is said to be the explanation of the disappearance. In the present case there was an abnormally long persistence of antibodies in the serum of the child. This may, of course, partly be explained by the fact that the initial titre of antibodies was high, and therefore they could be expected to persist for a longer time than usual. But this can hardly be the full explanation. It is to be noted that there were no signs of red cell production in the child until she was about 2½ months old. After this the antibody titre definitely disappeared. Therefore, in the present case the persistence of antibodies might be attributed also to an inhibition of the red cell production.

On the second admission the child had a severe anemia. After the transfusions the hemoglobin concentration decreased almost linearly during a 3 week period (Fig. 1). From the slope of this line the life span of the red cells was roughly estimated to be 6 weeks, these cells presumably being transfused red cells. The absence of reaction of the red cells against anti-D-serum supports this interpretation. When the child was 2½ months old there was a peak in the reticulocyte values indicating increased erythropoiesis; this was also reflected as a break in the curves of the hemoglobin concentration and the red cells (Fig. 1).

The subnormal survival time of the transfused red cells might be explained by the production of antibodies by the child itself; this would also be a contributing

cause to the fact that it was possible to demonstrate antibodies during such a long time after birth. Unfortunately this problem was not more closely studied.

A possible explanation of the absence of the child's own cells in the peripheral circulation on the second admission might be that newly formed red cells are promptly destroyed by antibodies as they reach the circulation. In 1955 Gasser reported a "pseudoaplastic anemia" as a special profile in hemolytic disease of the newborn, in which anemia was combined with a complete absence of reticulocytes; the antibodies were said to destroy not only the mature erythrocytes but also the reticulocytes. Contrary to the findings in the present case, however, the bone marrow in this case showed signs of an erythroid hyperplasia. Giblett *et al.* in 1956 described a case similar to the present case in which, in addition to the findings in the case related by Gasser, there was also a depression of erythropoiesis in the bone marrow.

It may, of course, be questioned whether in the present case the transfusions have appreciably suppressed the erythropoiesis. However, considering the amount of blood transfused, and in view of the course of the disease as a whole, this seems unlikely to be the case (cf. Giblett *et al.*, 1956).

In the present case and in the cases reported by Giblett *et al.* the antibody titre was initially very high. A similar case is also described by Wiener *et al.*

initially high antibody titre. It is difficult to say if such a high titre might have an inhibiting effect on erythropoiesis. Giblett *et al.* (l.c.) assume that the antibodies (1952), in which a protracted course over more than 2 months was related to an under such conditions may affect not only the cells in the peripheral circulation, but also the red cell precursors in the bone marrow. Another possible explanation of the decreased bone marrow function may be that this is the result of an exhaustion. This is in line with what Owren (1948) has assumed under certain circumstances to be the cause of the acute crises in congenital hemolytic anemia. The disappearance of antibodies from the serum which in the present case was observed at the same time as the reticulocyte peak, would thus be a sign of regeneration of red cell production. At present it cannot be decided which of the two theories presented above is the most probable explanation of the prolonged anaemia observed in this type of hemolytic disease of newborn. Further investigations on similar cases may give more information about this problem.

Summary

A case of hemolytic disease of the newborn is reported in which about 6 weeks after birth there developed a severe anemia which apparently was due to decreased bone marrow function. The pathogenesis of this is discussed.

Hypofonctionnement de la moelle osseuse dans l'ictère hémolytique du nouveau-né. Description d'un cas avec anémie sévère et persistance prolongée des anticorps.

Description d'un cas d'ictère hémolytique du nouveau-né dans lequel une anémie sévère fit son apparition au bout de 6 semaines après la naissance. Cette anémie était probablement due à un hypofonctionnement de la moelle osseuse. Discussion de la pathogénie de cette affection.

Herabgesetzte Knochenmarkfunktion bei hämolytischer Krankheit Neugeborener. Mitteilung eines Falles mit schwerer Anämie und langem Fortbestehen von Antikörpern.

Ein Fall von hämolytischer Krankheit Neugeborener wird mitgeteilt, bei welchem eine

schwere Anämie 6 Wochen nach der Geburt einsetzte. Die Anämie war anscheinend auf herabgesetzte Knochenmarkfunktion zurückzuführen. Die Pathogenese davon wird erörtert.

Hipofunción de la médula ósea en la enfermedad hemolítica del recién nacido. Comunicación de un caso con anemia grave y persistencia prolongada de anticuerpos.

Se presenta un caso de enfermedad hemolítica del recién nacido en que se desarrolló una anemia grave 6 semanas después del nacimiento. La anemia se debía aparentemente a una hipofunción de la médula ósea. Se discute su patogenia.

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Pediatric Clinic
Barnsjukhuset
Göteborg
Sweden

CASE REPORT

Chronic Vitamin A Poisoning

by ARNLJOT DRABLÖS and JOHANNES SLÖRDAHL

From Fylkessjukehuset, Aalesund, Norway, Pediatric and Roentgen Department

The toxic effect of large doses of vitamin A upon animals has been recognized since the 1920's. Long before that, Eskimo and polar travellers knew that liver from polar bears and other arctic animals was poisonous to men and animals. Rodahl & Moore, 1942, found enormous amounts of vitamin A in the livers of polar bears, thus disclosing vitamin A as the possible cause of the toxic effects of this liver. Later, Rodahl showed in experiments carried out in rats that polar bear liver and large doses of vitamin A produced identical toxic effects and that polar bear liver from which the vitamin A was removed did not produce symptoms of toxicity. The toxic effects of vitamin A upon rats and other animals has been confirmed later by several other investigators (10, 17). The chief symptoms are cessation of growth, falling hair, spontaneous fractures, dry and vulnerable mucous membranes and hemorrhages. This increased tendency to bleeding is the result of reduced prothrombin level which can be curtailed by administration of vitamin K (10).

Chronic vitamin A poisoning in humans was first reported in 1944 by Josephs, in a

child almost 3 years old, who from an age of 2-3 months had been given 200,000-300,000 I.U. of vitamin A daily. In the years following there were several reports from America of chronic vitamin A poisoning in children (1, 2, 3, 5, 6, 14, 16, 18). All these children had been given large doses of vitamin A-D concentrate over a period of several months. The doses administered varied between 75,000 I.U. and 500,000 I.U. of vitamin A daily for at least 6 months, and all the children except one [ref. (1)] were over 1 year of age at the time the diagnosis was made.

A few cases of chronic vitamin A poisoning in adults have been published in America since 1951 (4, 15). Very few reports of vitamin A poisoning have been reported in Europe.

Pickup, 1956, published the first two cases in Great Britain, both in children, 4 and 6 years of age. In contrast to the American cases of hypervitaminosis A, these patients had been given pure vitamin A concentrate. The symptoms are: After several months of large doses of vitamin A the child becomes increasingly irritable, has anorexia and pruritus and does not appear to thrive. Older children always complain of pain in the extremities. The skin becomes dry and itching, and there is often a rash-like eruption. The lips are cracked and sore with bleeding rhagades. Loss of hair is common. A little later firm, tender swellings appear in the soft tissues over one or more of the long

bones, most frequently the metatarsals or forearms. Roentgen examination of the skeleton in the affected parts shows characteristic periosteal changes with thick, protruding cortical layer, described by Caffey as "cortical hyperostosis". Increased tendency to bleeding is often found clinically, but there are no definite pathological findings in the bleeding, coagulation- or prothrombin-time in children up to the present (8). Normal electrolyte values are found in the serum. Alkaline phosphatase is routinely high in children, while in adults the values are normal. The serum lipoids were found to be increased in several cases. The most important factor in the diagnosis, however, is a markedly increased vitamin A level. The condition is further characterized by the rapid cessation of all clinical symptoms (except the roentgenological) following discontinuation of the vitamin A. The diagnosis is made in most cases between the ages of 2 and 3, but many of the patients had symptoms earlier.

Acute hypervitaminosis A was first observed in the polar districts after eating liver from the polar bear and other arctic animals. The symptoms commence from 4-8 hours after the meal with headache as the dominating symptom. Nausea, vomiting, dizziness and irritability follow, succeeded by drowsiness and a compulsive need for sleep. These symptoms are frequently followed by patchy or generalized peeling of the skin (8, 12). Acute vitamin A intoxication in children was first reported by Marie & Sée, 1951, in 3 children, 7½, 3½ and 3 months of age, who had received 350,000 I.U. of vitamin A combined with 300,000 I.U. of vitamin D within 24 hours previous to the onset of the symptoms. In addition to vomiting, restlessness and drowsiness bulging of the fontanel was an outstanding symptom.

Case Report

S. B., male, born Dec. 8, 1955, was referred to a pediatrician on July 11, 1956, because of a swelling of the right foot and was admitted to the Hospital on July 16, 1956,

for observation. Pregnancy and delivery were normal; birth weight 3400 g. The baby was well and appeared normal during the neonatal period and the first few months. He was vaccinated with BCG vaccine post partem (right thigh). Swelling of the glands of the right groin appeared after a few weeks, followed by suppuration and subsequent spontaneous healing without specific treatment. The baby was given artificial feeding (cow's milk formula) from birth. From 2 to 4 months of age 10 ml of "Sanasol" was given daily, a dose of approximately 5000 I.U. vitamin A, 500 I.U. vitamin D, 30 mg vitamin C and 1 mg vitamin B₁. At the age of 4 months A-D vit. drops "AFT" were given (containing approximately 30,000 I.U. vitamin A and 6000 I.U. vitamin D per g). This was said at the first questioning to have been given according to the doctor's orders twice daily. During the weeks preceding the consultation the patient had shown signs of decreasing well-being with increasing anorexia, behaviour changes, irritability, itching of the skin and marked inactivity, and in the latter 10-12 days an increasing swelling, extremely tender to touch, appeared on the lateral side of the right foot.

Findings on admission: Length: 71 cm, weight 8500 g. He was whining and had a yellowish pale facial coloring. Temperature: 37.7°C. Pulse: 120, regular. The head appeared large in relation to the body and had a circumference of 47 cm. The fontanel was large, 7 × 6 cm, without definite bulging. Marked craniotabes was present over the entire cranium, which could be pushed in like a ping-pong ball anywhere. The eyes had a vacant stare and appeared "hydrocephalic" with a visible scleral border over the cornea. The skin was dry. Many scratch marks were seen on the trunk, and a light, rash-like, macular eruption was present.

There were no visible signs of bleeding in the skin or mucous membranes, nor loss of hair. The lips were very dry and scaly with small fissures close together. A large, firm, extremely tender swelling, without redness

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Fig. 1. Detachment of the periosteum of the 5th r. metatarsal from the proximal to the distal end, and of the 4th r. metatarsal around the proximal end. Dense zone across the proximal half of the 5th r. metatarsal with slight angulation.

or heat of the skin, was seen laterally on the right foot over the 5th metatarsal. The swelling was not adherent to the skin, but seemed fixed to the tissues beneath. A similar, much smaller swelling was found over the 5th metatarsal on the left foot. Examination of the other organs revealed nothing pathologic. Blood examination: Hb 88% (Sicca), erythrocytes 4.58 mill., index 0.95. W.B.C. 7500, differential count normal. There was moderately increased bleeding time ($8\frac{1}{2}$ min) and prothrombin time (80% according to Owren's method). Thrombocyte count and coagulation time were normal. (One week after the first tests the prothrombin time was 95% and the bleeding time normal.) Normal values for calcium and phosphorus were found in the serum, while alkaline phosphatase was increased to 19 U. Bodansky. Two serum specimens were sent

to laboratories in Oslo for vitamin A analysis, but due to unfortunate circumstances the specimens were not examined. Repeated urin analyses showed negative reactions for proteins, blood, sugar and calcium (Sulkowitch), good specific gravity up to 1030 and negative microscopic findings. Blood urea was 42 mg/100 ml and BP was normal at around 80/45. Spinal puncture: Clear fluid under greatly increased pressure. Cells: 0. Nonne, Pandey and Weichbrodt's reactions: neg. Heller in 1/5 dilution: neg. Pirquet + (BCG vaccinated). Serum reactions for syphilis (mother and child): neg.

Roentgen examination showed detachment of the periosteum from the proximal to the distal end of the right 5th metatarsal (Fig. 1) and of the right 4th and the left 5th metatarsals around the proximal ends. The periosteal shadow appeared to lie convexly around the metatarsals and to be separated from them by a clear zone. The proximal halves of the metatarsals were crossed by a denser zone and a slight angulation was seen. This was interpreted as a sign of fracture. There was detachment of the periosteum of the right radius with radial angulation of the axis (Fig. 2). Protrusion of the periosteum was seen proximally in the left radius and distally in the left ulna. There was definite angulation of the left ulna distally, but not of the left radius. In the right ulna, there was probably angulation of the metaphysis. There was a swelling of the right clavicle which showed signs of periosteal detachment and thickening of the periosteum. Roentgen examination of the skull on July 17 showed an extremely thin-walled calvarium with markedly large fontanel, and with bulging of the soft tissues at the fontanel. Roentgen examination of the other parts of the skeleton showed no definite signs of pathologic changes. Roentgen examination of the kidney regions showed no sign of calcifications.

The clinical picture indicated the probability of a vitamin A intoxication very strongly. The grandmother who had cared for the child was called in for another conference on July 21. She then admitted that

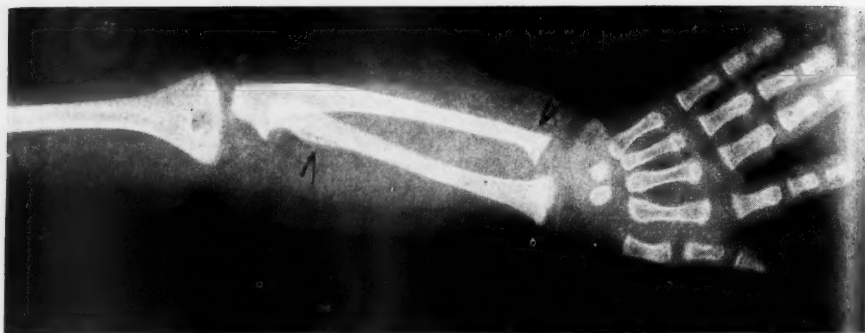


Fig. 2. Detachment of the periosteum of the right radius at the proximal end. Probably angulation of the right ulna at the distal end.

the A-D vit. drops had been given by pouring a portion from the bottle into the milk mixture or the cereal by guess twice daily. In the course of 100 days the patient had been given approximately 265 g A-D vit. drops, an average of 80,000 I.U. of vitamin A and 16,000 I.U. of vitamin D daily.

The A-D vitamin preparation was discontinued upon admission, and after one week the patient's symptoms had begun to subside. The itching and skin eruption disappeared together with the irritability and altered disposition. The swelling of the foot was greatly reduced, the tenderness gone and the patient began to move arms and legs normally. However, there was little improvement in the appetite during the three week's hospitalization, and the weight had decreased to 7550 g at the time of discharge. The lesions on the lips were almost gone after 3 weeks. Most remarkable were the rapid changes in the head: There was an almost palpable increase in the firmness of the skull each day. After 3 weeks the craniotables was barely palpable in the parietal regions only, and after 5 weeks, when a check-up examination was made in the out-patient department, there was no sign of craniotables. The fontanel, which was firm and tight upon admission, began to sink after 1-2 weeks, and by the end of the 3rd week appeared as a large depression in the cranium, as though the covering had become

too large for the contents. The circumference of the head was as follows: July 7, 16 and August 2: 47 cm. At discharge August 8: 46.5 cm. Out-patient department check-up: Aug. 17, 46.5 cm; Sept. 20, 47 cm (weight 9670 g); Oct. 18, 47.5 cm; Nov. 23, 48 cm. At the last two check-ups the eyes looked natural and the scleral border was no longer visible over the cornea. The patient's general condition was excellent with good gain in weight.

Roentgenographic follow-up: The denser zone across the affected metatarsals gradually became more marked, and the clear zone between the periosteum and the affected metatarsal showed increasingly more contrast. The protrusion of the periosteum decreased and the periosteum approached the bone beneath more closely. In the right arm periosteal shadow isolated from the underlying bone was seen in the proximal end of the radius until Sept. 19, and there was visible angulation of the bone which remained barely visible in the film taken on Dec. 12. Normal contours in the distal end of the right ulna returned gradually, simultaneously with the increasing calcification of the bone and disappearance of the osteoporosis seen earlier. The changes in the proximal end of the left radius and the distal end of the left ulna also disappeared gradually. The film taken Oct. 19 showed periosteal detachment in the 5th left meta-

carpal where none had been seen in the earlier roentgenograms. It appeared that these changes had developed some time after the overdosage of vitamin A had ceased. The cortical hyperostosis of the right clavicle was most marked at the examination made on Oct. 19 and remained at the examination on Dec. 8. Cortical hyperostosis of the right tibia was seen in the roentgen examination made on Sept. 1 and remained clearly apparent at examination on Oct. 19. The changes occurred after discontinuation of the vitamin A. Check-up examination on Aug. 8 showed that the bulge of the fontanel had subsided leaving depression instead.

Comments and Discussion

The information in the case history of a daily dose of 80,000 I.U. of vitamin A for 100 days, the typical clinical symptoms, anorexia and cessation of thriving, irritability, skin and lip symptoms, tenderness and swelling over the 5th metatarsal together with the characteristic roentgenological findings, the transitory hydrocephalus with craniotabes and the rapid regression of symptoms after discontinuation of the A-D vit. drops confirm the diagnosis in the authors' opinion. The primary alternative in a differential diagnosis is infantile cortical hyperostosis, a condition which according to Caffey has previously been mistaken for hypervitaminosis A in several instances. The former condition always appears in the course of the first 4 months of life, is a febrile disease markedly affecting the general condition and lasts if untreated for weeks or months. In infantile cortical hyperostosis the mandibles are always affected, while they are never affected in hypervitaminosis A. Conversely infantile cortical hyperostosis has never been observed in the metatarsals where cortical changes are fre-

quent in hypervitaminosis A. The presence of hypervitaminosis D might also be discussed, as the patient received a relatively large dose of this vitamin (16,000 I.U. daily). However, toxic symptoms are very rarely seen after this dosage. In the many cases of hypervitaminosis A after vitamin A-D concentrate no clinical symptoms of vitamin D intoxication have ever been observed. The present case had no symptoms of vitamin D intoxication. Tuberculosis after BCG vaccination was considered only in the first analysis but could be excluded after roentgen examination and the further clinical course. The same may be said for the possibility of syphilis. Scurvy may produce tenderness and bone changes which clinically may be similar to those found in this patient up to a point. However, the clinical symptoms of bone tenderness and increased bleeding tendency disappeared very rapidly without administration of vitamin C.

The latent period from the time the large doses of vitamin A began until the clinical symptoms became manifest is markedly shorter in the present case than in cases described earlier, despite the fact that the dose was not more than 80,000 I.U. daily. This rapid appearance of symptoms may possibly be explained in that the "A-D vit. drops" are soluble in water and therefore perhaps more readily resorbed by infants than the oil concentrates. However, the individual vitamin A tolerance is unquestionably highly variable. One of the most interesting symptoms in this patient was the chronic hydrocephalus and the marked craniotabes. To the authors' knowledge the occurrence of hydrocephalus has not been emphasized previously in chronic hyper-

vitaminosis A. However, Gribetz *et al.* mention that one of their patients, a girl 17 months old, had an increased circumference of the head and that pneumoencephalography showed a slightly enlarged ventricle system. Arena *et al.* also mention that their patient, aged 6 months, had marked craniotabes and head circumference of 47 cm. Knudson & Rothman, who comment upon these cases in their excellent review article, interpret them as a "connecting link between the acute and chronic form" and assume that both these children had increased intracranial pressure with resulting hydrocephalus. In the present case it is natural to assume that craniotabes resulted from the hydrocephalus. This view is supported by the rapid regression of the craniotabes, which disappeared parallel with the symptoms of hydrocephalus (while the changes in the other bones remained considerably longer). The localisation of skeletal changes to the bones under mechanical stress is discussed by Caffey. In small children who cannot walk the forearms and metatarsals are probably the parts of the extremities most liable to trauma. Neither Caffey nor others claim that the changes seen in the bones result from fractures. The bone changes demonstrated in roentgen examinations in the present case with bands or zones of increased contrast crossing the bones and distinct angulation indicate fractures very strongly. In other bones in which the periosteum is seen to be detached from the bone there is no definite roentgenologic indication of fracture even though the picture is entirely similar to that seen in some cases of "green stick

fracture". However, these changes may be the result of subperiosteal hemorrhage.

Subperiosteal hemorrhage has been demonstrated by Rodahl in experimental cases without distinct roentgenological signs of fracture. Microscopy has shown subperiosteal blood clots and in a few of these cases also fracture of a few trabecula and irregular bone structure. Wolbach found in his experiments a regular increase in prothrombin time and bleeding time. Rodahl states that he has observed limping and signs of pain in the extremities in experimental animals which showed neither fractures roentgenologically nor sign of subperiosteal hemorrhage. The point may be raised that fracture may exist without being seen roentgenologically, or that limping and pains are symptoms in advance of the fracture.

Summary

After a short review of hypervitaminosis A, the authors describe a case of chronic vitamin A poisoning in a 7-month-old boy in whom the symptoms were manifest after 100 days of administration of approximately 80,000 I.U. of water-soluble vitamin A daily. In addition to the usual, well-known symptoms, a chronic hydrocephalus accompanied by marked craniotabes was observed. The development of craniotabes and the "cortical hyperostosis" changes in the bones are discussed. Craniotabes is interpreted as a result of the hydrocephalus present, and the roentgenologic changes in the bones are interpreted as the results of fractures and subperiosteal hemorrhage.

Intoxication chronique par la vitamine A.

Description d'un cas d'intoxication chronique par la vitamine A chez un bébé mâle de 7 mois chez lequel les symptômes devinrent manifestes au bout de 100 jours d'administration d'environ 80000 U.I. de vitamine A hydrosoluble par jour. En plus des symptômes habituels bien connus, le patient présentait une hydrocéphalie chronique accompagnée d'un crâniotabes marqué. L'auteur examine la pathogénèse du crâniotabes et des altérations « d'hyperostose corticale » des os. Le crâniotabes est attribué aux conséquences de l'hydrocéphalie existante et les altérations radiologiques des os sont interprétées comme étant le résultat de fractures et d'hémorragies sous-périostiques.

Chronische Vergiftung mit Vitamin A.

Bericht über einen Fall von chronischer Vitamin A Vergiftung bei einem 7 Monate alten Knaben, bei welchem die Symptome sich nach 100 Tagen von Verabreichung von ungefähr 80000 I.E. eines wasserlöslichen Vitamins A täglich einstellten. Abgesehen von den gewöhnlichen wohlbekannten Symptomen wurde chronischer Hydrocephalus, der von einer auffallenden

Kraniotabes begleitet war, beobachtet. Die Entwicklung der Kraniotabes und die Knochenveränderungen in der Form einer „kortikalen Hyperostose“ werden erörtert. Die Kraniotabes wird als Ergebnis des vorhandenen Hydrocephalus und die radiologisch nachweisbaren Knochenänderungen als Resultat von Frakturen und subperiostalen Blutungen gedeutet.

Intoxicación crónica por vitamina A.

Presentación de un caso de intoxicación crónica por vitamina A en un niño de 7 meses, en que los síntomas aparecieron aproximadamente a los 100 días de la administración de 80000 U.I. diarias de vitamina A hidrosoluble. Además de los síntomas habituales, bien conocidos, se observó una hidrocefalia crónica acompañada de marcada craneotabes. El desarrollo de craneotabes y las alteraciones óseas de « hiperostosis cortical » son objeto de discusión. Se considera la craneotabes como el resultado de la hidrocefalia existente, y las alteraciones roentgenológicas de los huesos se interpretan como la consecuencia de fracturas y hemorragias subperiostales.

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Fylkessjuehuset
Ålesund, Norway

Meconium Peritonitis

by A. ATTRAMADAL and KR. HARNÆS

From Institutt for Patologisk Anatomi, Rikshospitalet, Oslo (Head: Prof. Olav Torgersen, M.D.), and from Barneklínikken, Rikshospitalet, Oslo (Head: Prof. Leif Salomonsen, M.D.)

Although peritonitis in the new-born was formerly considered very rare, the condition has been described with increasing frequency in recent years. Rickham (1) states that in 17 per cent of the cases admitted to a pediatric surgical service, with symptoms of congenital intestinal obstruction, the cause was peritonitis.

Peritonitis in the new-born occurs in two main forms: acute bacterial peritonitis and meconium peritonitis. Of Rickham's 17 cases of peritonitis in the new-born, 10 were described as bacterial peritonitis and 7 as meconium peritonitis.

Meconium peritonitis is regarded as an aseptic chemical peritonitis caused by the passage of sterile meconium into the peritoneal cavity through an intestinal perforation (3, 5).

Although the condition has been known for many years, a certain confusion on this subject is still evident in the literature. This is chiefly due to varied nomenclature. Such names as foetal peritonitis, intrauterine peritonitis, and peritonitis in the new-born having frequently been used. These terms, however, have also included cases of bacterial peritonitis. The term meconium peritonitis should be used in those

cases only where the presence of meconium elements such as epithelial cells, mucus, lanugo hairs and bile pigments can be demonstrated in the peritoneal cavity. Because of the aseptic and prolonged course, the pathological picture shows changes of a rather chronic nature with infiltration of macrophages and giant cells. Another important feature is the marked fibrosis evidenced by extensive adhesions.

The passage of meconium into the peritoneal cavity can only take place through an intestinal perforation. Meconium is a sterile mixture of bile, desquamated epithelium, swallowed amniotic fluid, mucus and intestinal secretions. In the peritoneal cavity meconium will produce a sterile chemical peritonitis. Meconium begins to accumulate in the gut as early as the 3rd to 4th month of gestation, and at this stage, therefore, meconium peritonitis can theoretically develop. Thus a case of meconium peritonitis is described in a 6 months' old foetus (Rudnew, quoted by Rickham).

The clinical and pathological findings by meconium peritonitis depend upon the foetal age at which the intestinal perfora-

tion takes place and whether or not the perforation closes before delivery. However, if the perforation takes place during or immediately after delivery a picture of meconium peritonitis cannot be distinguished because the peritoneal cavity within few hours becomes invaded by bacteria. These are borderline cases and should not be considered as meconium peritonitis even if meconium elements can be found in the peritoneal cavity. On the other hand, if the perforation closes before bacterial contamination takes place, meconium peritonitis will develop. Antenatal closure of the intestinal perforation has frequently been described in literature (3, 6). Thus in 6 of Rickham's 7 cases of meconium peritonitis, no signs of perforation could be found.

In most cases of meconium peritonitis a clear cause of the intestinal perforation can be found, obstruction of the bowel caused by intestinal atresia or stenosis, malrotation, meconium ileus, etc., being the most frequent causes. Enteritis with necrosis of the intestinal wall and syphilitic ulcerations may also cause intestinal perforation.

However, in some cases no cause of the intestinal perforation can be found. The aetiology and pathogenesis of the "spontaneous" intestinal perforations in these cases are obscure, several theories such as trauma, congenital defects and circulatory disturbances of the bowel wall having been suggested (3, 2, 4.).

During the last few years we have observed three cases of meconium peritonitis; these cases will be reported.

CASE 1, S. E.—The patient was a five-day-old boy, weighing 4000 g at birth. At delivery

it was observed that the umbilical cord was macerated and the umbilicus dark and protruding. From birth onwards there was an increasing abdominal distension and by the second day fever and vomiting developed. No meconium passed. At admission to the Hospital the infant was prostrated and jaundiced. The abdomen was tense at palpation and severely distended with numerous distended veins crossing the epigastrium. No peristaltic sounds were audible on auscultation. Haematological examination revealed a leucocytosis of 25,800 white blood cells with a marked shift to the left. The blood culture was negative. X-ray examination of the abdomen (Fig. 1) showed abundant fluid and gas in the peritoneal cavity indicating intestinal perforation. Additionally, numerous peritoneal calcifications were observed.

At laparotomy, performed when the boy was six days old, large quantities of purulent fluid and gas were found in the peritoneal cavity. The stomach and intestines were adherent to each other and to the posterior abdominal wall by fibrinous and firm fibrous masses which were impossible to free. The infant died on the first postoperative day.

At *autopsy* the visceral and parietal portions of peritoneum were found to be covered by a thick and dark green fibrinous layer. These findings were particularly prominent around the umbilicus and the umbilical vessels. There were fibrous adhesions between nearly all the intestinal loops. No intestinal perforation could be demonstrated. Sections from the abdominal wall as well as from the intraperitoneal portion of the umbilical vein and the intestines showed by microscopic examination a considerable deposit of fibrin and fibrosis of the peritoneum. The fibrin and fibrous tissue were both infiltrated with a large number of polymorphonuclear granulocytes, lymphocytes and macrophages. Furthermore, there was a heavy deposit of squamous epithelial cells and a considerable amount of calcium salts (Fig. 2). Mucicarmin-stained sections showed abundant mucus. The histology of the mucosa and muscular layers of the intestines was normal.

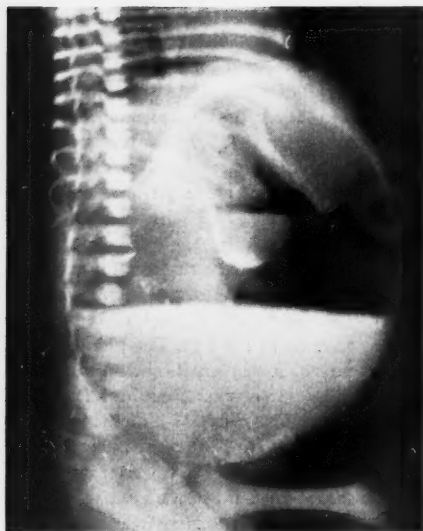


Fig. 1 (Case 1). Radiogram showing fluid and gas in the peritoneal cavity and peritoneal calcifications.

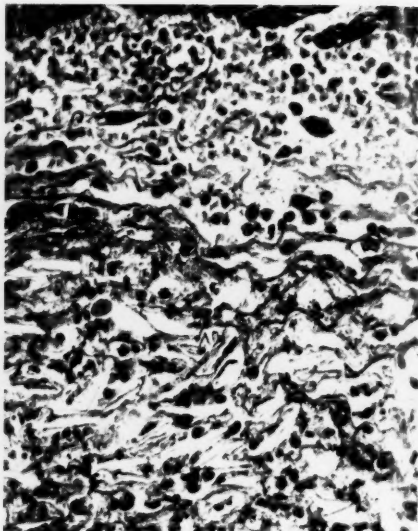


Fig. 2 (Case 1). Photomicrograph showing a thickened peritoneum with heavy deposits of squamous epithelial cells. H.E. $\times 400$.

CASE 2, M. S.—The patient was a girl weighing 2950 g at birth. On the first day of life there developed an increasing distension of the abdomen with prominent dilatation of the veins. On admission the infant was prostrated and vomited bile-stained fluid. No meconium was passed. X-ray examination of the abdomen showed a picture of intestinal obstruction with gas in the peritoneal cavity. Additionally, intraperitoneal calcifications, indicating the presence of meconium peritonitis, were demonstrated. At the operation, performed when the patient was $1\frac{1}{2}$ day old, the intestines were found to be adhering together forming a large mass located in the right iliac fossa. A constriction of the gut, about 2 cm from the ileo-coecal junction, had caused a considerable distension of the distal portion of the ileum which presented several small perforations. Intestinal resection was performed. The infant died on the first post-operative day.

The resected intestine was found to be of irregular diameter and wall thickness. Por-

tions of the intestine were markedly constricted and in some areas small diverticular structures were seen. Microscopy showed a mainly normal intestinal wall, but in one area the longitudinal muscular layer was found to be totally absent; and the circular layer was thin and atrophic (Fig. 3). Areas were also found where the intestinal wall was necrotic with haemorrhages and heavy leucocyte infiltration (Fig. 4). In another area the whole intestinal wall was replaced by granulation tissue in which there were deposits of squamous epithelial cells, mucus, calcium salts and an unspecified brown substance (Fig. 5). Additionally, there was a considerable infiltration of lymphocytes and macrophages.

At autopsy 75 cc of bloodtinged fluid were found in the abdominal cavity. On both the parietal and visceral portion of peritoneum there were deposits of yellow-green fibrin adhering the intestinal loops together. Microscopic examination revealed abundant leucocyte infiltration, particularly polymor-



Fig. 3 (Case 2). Photomicrograph from ileum showing absence of the longitudinal muscular layer and a thin atrophic circular layer. H.E. $\times 25$.



Fig. 4 (Case 2). Photomicrograph from ileum showing necrosis of the intestinal wall which is heavily infiltrated with leucocytes. H.E. $\times 180$.

phonuclear granulocytes, in the fibrin layer. Deposits of meconium elements or calcium salts could not be detected.

CASE 3, M. S.—The patient was a boy with birth-weight 2950 g. At birth no abnormality was observed, but by the second day gross distension of the abdomen became apparent with prominent dilated superficial veins. Clinical examination revealed marked prostration and frequent vomiting of bile-stained fluid. No rigidity or spasm was felt on palpation of the abdomen, nor were any peristaltic sounds heard on auscultation. Haematological examination revealed no leucocytosis. Clinically peritonitis was suspected. The patient died when 5 days old.

At *autopsy*, 100 cc of yellow-green purulent fluid was found in the peritoneal cavity.

The parietal and visceral portion of the peritoneum was covered with fibrin and the intestinal loops were distended, adhering to each other as well as to the stomach and colon. No perforation of the gut could be detected. Microscopically the peritoneum was found to be covered with fibrin, heavily infiltrated with leucocytes, principally lymphocytes and macrophages (Fig. 6). Additionally, the fibrinous layer was found to contain squamous epithelium together with a yellow-green substance, giving positive reaction for bile by the Stein test. Deposits of mucus and calcium salts were also observed. In some areas development of granulation tissue was detected. The histology of the mucosa and muscular layers was normal.

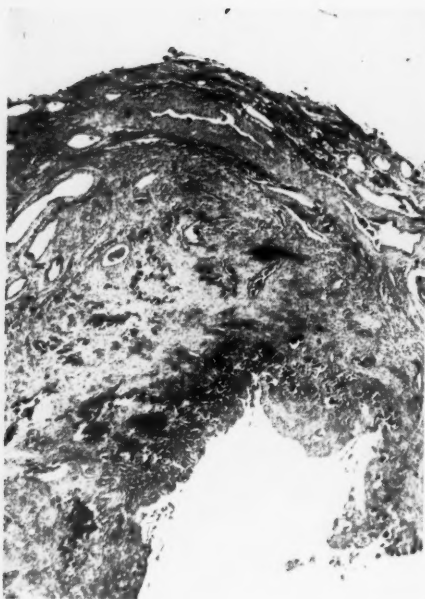


Fig. 5 (Case 2). Photomicrograph of an isolated area of ileum where the whole intestinal wall is replaced by granulation tissue. Abundant deposits of calcium. H.E. $\times 180$.

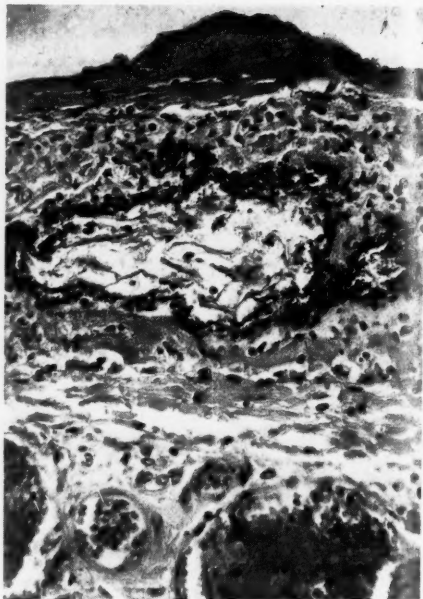


Fig. 6 (Case 3). Photomicrograph showing a thickened peritoneum covered with fibrin. In a small cavity deposits of squamous epithelial cells and a substance giving positive reaction for bile salts. Stein test. $\times 320$.

Discussion

In the cases referred the condition manifested itself by signs of intestinal obstruction, abdominal distension, bile stained vomiting and delayed passage of meconium. In Cases 1 and 2 the clinical diagnosis of intestinal obstruction was confirmed by radiography. Furthermore, in both cases the detection of intraperitoneal calcifications suggested the diagnosis of meconium peritonitis, which in all three cases was verified by histologic examination. Although these three cases had common features, they differed in certain clinical and pathological aspects. These differences seemed to depend on: (1) the foetal age at which the intestinal perforation had taken

place; (2) whether or not the perforation had closed spontaneously, and if so, at what age; (3) the secondary changes produced by the peritonitis.

In Case 1 histological examination revealed a considerable proliferation of connective tissue with chronic and acute inflammatory changes. As the clinical signs of intestinal obstruction were already present at delivery, it must be presumed that the intestinal perforation which had caused the development of meconium peritonitis, had taken place in utero. The acute inflammatory changes, on the other hand, make it presumable that the intestinal perforation was still open at birth and

that secondary bacterial peritonitis was superimposed. The intestinal perforation could not be detected at autopsy, presumably due to the abundant deposits of fibrin.

In Case 2 the clinical signs and X-ray findings made the diagnosis of meconium peritonitis probable. The findings at operation and the histology of the resected intestine verified the diagnosis. Furthermore, the resected intestine showed several perforations and microscopy revealed necrosis with acute inflammatory changes. Examination of the remainder of the peritoneal cavity, at autopsy, merely revealed signs of acute peritonitis. One must here presume that the condition had run a dual course. Firstly, the histology of the resected intestine shows that possibly there has been an intestinal perforation in utero which has closed antenatally, but which has been the cause of a circumscribed meconium peritonitis. Secondly an intestinal obstruction has arisen after delivery causing necrosis and perforation of the intestinal wall with the superimposition of bacterial peritonitis.

In Case 3 the clinical picture was that of an adynamic intestinal obstruction, and suggested peritonitis. Autopsy revealed meconium peritonitis with signs only of chronic inflammation. As no intestinal perforation could be found, it seems logical to suppose that the perforation closed antenatally, thereby preventing the development of bacterial peritonitis. The purulent fluid found in the peritoneal cavity was possibly the result of a chemical peritonitis produced by the sterile meconium. Unfortunately, bacteriological examination of the fluid was not undertaken, but the relatively quiet clinical picture, and

the absence of leucocytosis suggest an aseptic peritonitis.

In Case 2 the defect in the muscular layer of the intestine might have been the cause of the perforation. In the other two cases referred no cause of the primary perforation was found. No malformation of the gut was revealed and the normal pancreas in both cases made a meconium ileus unlikely. In none of the cases was the intestinal perforation persistent at autopsy, except in Case 2 where there were perforations secondary to the adhesions caused by the meconium peritonitis. This is in agreement with the findings of other authors (3, 6).

The diagnosis of meconium peritonitis is very difficult, usually only presumptive and mostly verified at operation or autopsy. In most cases the clinical picture bears the characteristics of the obstruction which is responsible for the intestinal perforation. In the cases reported above the principal signs were: bile-stained vomit, absent or scanty passage of meconium and marked abdominal distension without rigidity or muscular spasm. No peristaltic sounds were audible on auscultation, and in all cases there was a prominent dilatation of the superficial veins around the umbilicus and in the epigastrium, which can be explained on the basis of increased intraperitoneal pressure. If the intestinal perforation is persisting after birth, the infant will, additionally, develop signs of bacterial peritonitis. Signs of intestinal obstruction and possibly free gas and fluid in the peritoneal cavity may be demonstrated by radiography. According to White (7) intraperitoneal calcifications can be revealed by X-ray examination in 75 per cent of the cases. If the intestinal

perforation closes antenatally, thus preventing the superimposition of bacterial contamination, a meconium peritonitis may later on manifest itself by an intestinal obstruction, secondary to the adhesions.

The treatment of meconium peritonitis is surgical, the aim being to relieve the intestinal obstruction as well as to close any open perforation. The prognosis is poor. Thus, even after operation for this condition, White (7) has recorded only 18 cases of survival from the literature.

Péritonite à méconium.

Communication relative à trois cas de péritonite à méconium ayant tous abouti à une issue fatale. L'auteur passe en revue leur pathogénèse et leur pathologie. Le diagnostic clinique est extrêmement difficile à établir, mais il convient de se rappeler de l'éventualité de cette maladie lorsqu'on se trouve en présence d'une obstruction intestinale chez un nouveau-né. Le pronostic est sévère, mais une intervention chirurgicale est parfois couronnée de succès.

Meconium Peritonitis.

Bericht über drei Fälle von Meconium Peritonitis, die alle tödlich abliefen. Die Pathogenese und Pathologie werden erörtert. Die klinische

Summary

Three cases of meconium peritonitis are reported, all of them with fatal outcome. The pathogenesis and pathology are discussed. The clinical diagnosis is very difficult, but the condition must be borne in mind when one is faced with a case of intestinal obstruction in a new-born. The prognosis is bad, but surgical treatment may be successful.

Diagnosestellung ist sehr schwierig, aber man muss sich diesen Zustand vor Augen halten, wenn man mit einem Fall von Darmverlegung bei einem Neugeborenen konfrontiert ist. Die Prognose ist schlecht, aber chirurgische Behandlung könnte erfolgreich sein.

Peritonitis por meconio.

Son relatados tres casos de peritonitis por meconio, todos ellos de terminación fatal. Son discutidas su patología y patogenia. El diagnóstico clínico se muestra difícil, pero esta entidad deberá ser tenida en cuenta frente a todo caso de obstrucción intestinal del recién nacido. El pronóstico es malo, pero el tratamiento quirúrgico puede ser exitoso.

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Pediatric Clinic
Rikshospitalet
Oslo
Norway

PROCEEDINGS OF PEDIATRIC SOCIETIES

Swedish Pediatric Society

Meeting March 13, 1959

Olle Naglo: Listerellosis in the newborn.

The clinical course of Listerellosis is reported of a newborn, weighing 2070 g at birth. Normal pregnancy. Delivery was normal except for discharge of markedly meconium-tinged amniotic fluid. The child cried following suction. Placenta contained abundance of calcium. The child sustained repeated cyanotic attacks 5 hours after birth. Lowered tonus. Poor general condition. Slight icterus. C.S.F.: increased albumin, 6 monocytic cells. Culture: following enrichment, abundant growth of *Listeria*. Patient placed on tetracyclin, but succumbed 2 days old.

Per-Henrik Magnusson: Bacteriology in Listerellosis in the newborn.

The following examinations were made in the above-mentioned case. C.S.F. sample was removed on second day of life. Direct Gram-stain preparation revealed no bacteria. Simultaneous seedings of sample on solid media and in a few broth tubes which were incubated at 37.5°C for 24 hrs and in turn seeded out on solid media. Growth was obtained, first after broth-enrichment, of some greyish-white beta hemolytic colonies. Gram-slides of these showed short, almost coccoid Gram-positive rods, simulating enterococci. Further 24 hrs' growth and the rods had become elongated and hence could not be mistaken for cocci. Colony-formation, morphology and fermentation reactions agreed with those reported in literature for *Listeria monocytogenes*. A broth culture was injected intraperitoneally into several mice, which died from peritonitis within 48 hrs. *Listeria* cultures were recovered from the

cadavers. Broth cultures were also instilled intraocularly in a rabbit and this produced marked conjunctivitis. Another rabbit was injected intravenously and this produced monocytosis. These experimental results all confirm the Listerellosis diagnosis.

Post-mortem material was removed from brain-tissue, umbilical cord and intestinal mucosa, but *Listeria* were recovered only from the brain tissue. Vaginal and blood samples were taken from the child's mother. The vaginal sample contained no *Listeria*. The mother's serum agglutinated with the *Listeria* strain. This was also agglutinated by other sera, and hence this cannot be ascribed any importance. The *Listeria* strain belonged to Group I. The mother's serum gave an antibody titer of 1/16 (normal value). A few further blood samples from the mother may be of interest for the diagnosis of an eventual alteration in titer during the follow-up period. The strain displayed good sensitivity for all the usual antibiotics.

Kersti Hedberg: Listerellosis pathology.

Listerellosis was first described in Sweden by Linell, Malmö. This also occurred in an infant in whom the *Listeria* infestation seems to occur ordinarily in man. Numerous small hemorrhages into the skin were seen at autopsy. The soft membranes of the brain were markedly hyperemic and groups of small circular faintly yellow foci were seen in close proximity to the vessels. The liver was diffusely peppered with pinhead-sized faintly yellow nodules. The adrenals presented numerous hemorrhages and likewise in the renal papillary pyramids. The lungs

disclosed numerous irregularly delimited hemorrhagic areas scattered among healthy alveolar tissue. Otherwise no unusual macroscopic changes. The histological examination revealed that the liver nodules (granulomata) consisted of proliferating hepatic cells, reticulocytes, and some lymphocytes. Moreover, the granulomata contained masses of Gram-positive short rods which took the silver impregnation of Levaditi's stain. The adrenals too contained a number of granulomata. The lungs showed granulomatous alterations of similar pattern. Examined parts of the brain disclosed meningitis and formation of granulomatous tissue. Sections from various parts of the intestinal tract revealed individual granulomata with ulcerated mucous membranes.

G. Sterner: Cold-agglutination ad modum Garrow—a single quick practical test.

DISCUSSION: *Greta Hedenström:* Garrow's test may be highly valuable in an acute disease situation. The following example may be offered. An older woman with inflammatory symptoms of the lungs was admitted to the Hospital for Epidemic Diseases in Stockholm. During the night she vomited large quantities of fresh blood. After repeated bloody vomits she grew quite exhausted and exsanguinated (Hb 5 g%). Blood transfusions seemed vitally indicated. By performing cross-agglutination blood-matching tests it became evident that agglutination took place regularly despite several flasks with fresh group-correct donor-blood being used. When cross-agglutination was performed at 37.5°C, however, agglutination failed to occur. Garrow's test was carried out with the patient's blood and turned out to be strongly positive. The earlier observed agglutination during the cross-tests was interpreted as a cold-agglutination and blood transfusion was administered. This produced no clinical complications.

B. Rönnerberg-Halvorsen: Hypoplastic anemia following carbutamide medication.

A serious complication following close upon carbutamide medication for diabetes

mellitus occurred in the Samariten Children's Hospital during the fall of 1958. A 5 year old boy, with newly detected diabetes, was admitted in August and treated with insulin and tolbutamide (Diabuton), 1 pill (0.5 g) \times 3. The boy's illness could henceforth be held in check solely by peroral treatment. But when fabrication of Diabuton was discontinued, this drug was replaced by a similar dose of carbutamide (Inbuton). Whereupon the boy was discharged from the hospital. Three weeks after commencing the carbutamide medication, the boy took ill at home, 3 days on a run, with fever, and a concurrent morbilliform exanthema, considered to have been provoked by the pills. The boy was promptly readmitted to the Hospital with ketonuria, and a grave anemia with a low Hb-level of 5.7 g% (37%) and 2.5 million R.B.C. The lowest W.B.C. 3000. Liver tests and serum iron normal. Sternal puncture showed inadequate bone marrow and extramedullary blood formation. The boy received blood transfusions, after which the blood values increased rapidly. The hypoplastic anemia was interpreted as a complication of carbutamide medication. Because of its toxicity one should avoid carbutamide medication for diabetes, and it is most important to conduct regular blood controls in connection with the peroral treatment of diabetes mellitus.

DISCUSSION: *B. Vahlquist:* One may pose the question whether the anemia represents the hypoplastic type, as stated in the title. Despite the low reticulocyte count, the final rapidly falling Hb. value suggests that there must have been a hemolytic component. The speaker justly emphasized the importance of regular blood controls. Perhaps it is still more important to impress upon the family the necessity to contact the physician directly whenever an indefinite fever and an exanthema occur. In the presence of such experience as mentioned here, it is questionable whether such medication is justifiable in juvenile diabetes, in view of the fact that the favorable benefit is limited.

A. J. W. Hagströmer: Protracted pregnancy intervals and mongolism.

If one investigates in a material of mongoloids and their normal siblings the long intervals between pregnancies and their eventual correlation to mongolism, it becomes necessary to make comparisons of approximately similarly aged mothers, equivalence and number of children in each lot. Moreover one should exclude the interval belonging to the most recently born child or to the children born after the arrival of the mongoloid child. No correlation exists in the present investigation between the long intervals of pregnancies and mongolism in the beginning (by low maternal age respective low parity), but definitely toward the end of the productive period (by high maternal age respective high parity). The observed difference between the beginning and the end of a woman's productive period makes a direct connection between the long intervals and mongolism improbable. A better hypothesis would appear to be that

the long intervals in the young mothers and in mothers who get children more often might be intentional and therefore also harmless. Long intervals in older mothers and in women having had many children might on the contrary oftener be an expression for a relative sterility. This situation and mongolism might thus be considered to partake of a common etiology. This latter hypothesis would appear to find support in the preliminary results of our investigation. More than 5000 women have responded during pregnancy to a questionnaire put forth by our Maternal Health Centers regarding whether or not pregnancy was desired. If it were desired, then they report about the approximate time when contraceptive measures were not employed. Among the desired pregnancies, 6 resulted in births of mongoloid children. All 6 belonged to that half of our material which required a long period (more than 6 months) to become pregnant.

Marcel d'Avignon, Stockholm

Pediatric Society of South Sweden

Meeting May 10, 1959

Per Selander: Asthmatic Symptoms in the First Year of Life. (Will be published in *Acta Pædiat.*)

Inge Ekström: Purpura Anaphylactoides and Streptococci.

During the period January 1949 to April 1959 55 patients with anaphylactoid purpura were treated at the Flensburg Children's Hospital in Malmö. Since the joint pains in many cases were pronounced, throat culture and/or antistreptolysin titration (ASL) were made in 33 cases. In 10 of the 26 specimens taken there were β -hemolytic streptococci. ASL was positive (250-1000 units) in 16 of 21 specimens taken. On account of the large number of positive specimens all (12) cases of anaphylactoid purpura during the period

January 1958 to April 1959 were examined with throat culture and ASL. Moreover, in addition to routine examinations of the blood and urine, electrophoretic examination of the serum has also been carried out. These showed in all cases an infection picture with an alpha-2 increase, usually also an alpha-1 increase and in half the cases an gamma increase. The throat culture was positive in 4 cases and ASL in 8. In the total number of cases from January 1949 to April 1959 the throat culture was positive in 37 per cent and ASL in 73 per cent of the specimens taken. The investigation thus speaks in favor of a connection between an infection—usually with β -hemolytic streptococci—and purpura anaphylactoides.

O. Wallengren: The Prognosis of Pyelitis in Childhood.

During the period 1949 to 1953 33 boys and 81 girls were admitted to the Flensburg Children's Hospital for treatment of pyelitis or cystopyelitis. These have been re-examined. Of these 100 have given anamnestic data concerning their state of health after the actual attack of pyelitis. Urine specimens have been obtained from 87 and in addition a physical examination has been made of 37. Two children have died. One patient had pyelitis at the time of the examination. The others said that they were well, and all the urine specimens examined were normal. Of the 100 re-examined patients 67 had had only one attack of pyelitis and are now completely healthy. Two have died from urinary tract diseases. Relapses have occurred in 31 cases, and of these 6 could be treated surgically. Of the others who have had relapses 14 have exhibited pathologic changes in the urinary tract on urography, while 11 have not displayed any abnormalities. This series of cases, which is probably representative of a Swedish children's hospital, yields considerably more favorable figures than those which have been reported in recent years from re-examinations in England and the United States.

Per Selander: Membranous Stomatitis. (Will be published in Acta pædiat.)

Margareta Isgren: The Prognosis of Paroxysmal Tachycardia and of Extrasystolic Arrhythmia in Childhood.

The cases are from the Flensburg Children's Hospital during the period 1947 to 1958. Only such cases have been included where at the time of treatment no etiology

of arrhythmia could be found. There were 8 cases of *supraventricular paroxysmal tachycardia*. Five of the patients were less than 1 year of age. Of these 4 exhibited affected general condition and symptoms of heart failure. Roentgen showed cardiac enlargement in 2 of the cases. The period of observation varied between 2 and 11 years. Of the patients 3 have had no relapses, 2 have not had symptoms for 1 year or more, whereas 2 girls, whose symptoms appeared first at 10 years of age, still have attacks. One patient died in infancy. On re-examination unipolar electrocardiogram showed a typical Wolff-Parkinson-White syndrome in 1 of the patients, suspected congenital heart disease in another. The other patients had normal electrocardiograms. Roentgenography of the heart yielded a normal picture in all patients. There were 11 cases of *extrasystolic arrhythmia*. Most patients prior to the onset of the arrhythmia had had an infectious disease, although all of mild character. At the time of treatment there were no signs of organic heart disease. All except 1 were in good condition, and the majority were not troubled by their arrhythmia. Electrocardiography revealed in 10 of the cases ventricular extrasystoles, the remaining cases had supraventricular extrasystoles. According to their parents 3 of the patients were emotionally unstable. On re-examination it was found that the majority did not have any symptoms. All except 1 had been completely healthy and were able to do all forms of bodily exercise. Electrocardiography showed in 3 cases persistent extrasystoles, but the period of observation in these cases was less than 2 years.

Per Selander, Malmö

BOOK REVIEWS

Brit. Medical Bulletin. Vol. 15, May 1959. The British Council, Davies Street 65, London. 174 pages. Price 20 shillings.

This is a symposium by 19 authors, each prominent in his field of blood research and contains everything worth knowing about blood groups, their clinical importance, inheritance, biochemistry, blood groups and disease, the relation between animal and human blood groups etc. Dr. A. E. Mourant of the Brit. Medical Research Council has acted as chairman of the Committee preparing the Symposium and Dr. K. L. G. Goldsmith as its Scientific Director. The very rapid progress in blood group research has made it difficult for clinicians to follow its development by studying the current literature and therefore it is a great advantage and very fortunate occurrence to have gotten this excellent summary of the actual knowledge about blood groups.

The Nephrotic Syndrome. Proceedings of the Ninth Annual Conference, edited by Jack Metcalf.

The National Nephrosis Foundation, Inc., New York, 1958. 248 pp., numerous figures and tables.

This monograph records the papers read and discussed at this conference of prominent investigators in this field of internal medicine, pediatrics and biochemistry. The subjects discussed relate to actual problems in the study of the nephrotic syndrome: antigens, antibodies, renal lesions, lipoprotein metabolism, electrolyte metabolism, work in progress and evaluation of steroid therapy. The report is very informative about contemporary work carried on by the assisting research workers in their laboratories and hospital wards on sundry aspects of the nephrotic syndrome. The evaluation of the steroid treatment of this disorder is of special

interest to clinicians. The verbally transcribed papers and discussions make the reading of the monograph highly entertaining and profitable.

Marcel Graffar: Cinq cent familles d'une commune de l'agglomération Bruxelloise.

Published by l'Institut de Sociologie Solvay, Bruxelles 1957, 103 pp. Price 95 fcs. Belg.

This monograph deals with the influence of the family and social environments on the growth and development of a group of children. The study forms a part of a coordinated investigation of the individual's longitudinal development which is being conducted in a number of countries (England, France, Switzerland, Sweden, Belgium in Europe, and in French West-Africa and Uganda in Africa, and Virginia in the U.S.A.) under the direction of the International Children's Centre in Paris. The author succeeded to include in this study 80% of all infants born within one year in a chosen suburban area. The total number was 504 families with 506 children. The natality rate was very low, only 11% (in all of Belgium 16.7%). Of special interest is the author's registration method into social classes by making use of five different criteria: occupation, theoretical education, economic standard, living-quarter standard and living-quarter location. Among the followed-up families, 5.1% belonged in the highest class (I), 13.6% in class II, 41.3% in class III, 36.8% in class IV and 3.2% in class V. The composition of this population corresponded rather well with the general conditions in all of Belgium. Only 2% of the mothers had had no prenatal control during pregnancy, and only 4% had been delivered at home. It is remarkable that the frequency of premature births was practically similar in the different social classes, 3.3-4.6% in

the 3 largest middle social classes. These 3 groups proved to have an equal distribution of work away from home. In a normal population the pregnant woman's work away from home is the only social factor which increases the risk of a premature birth. This study purports to be an initial orientation about the material and it is of considerable interest especially because of the discussion of the different social classes.

Klinische Methoden der Blutgerinnungs-analyse. J. Jürgens and F. K. Beller.

Georg Thieme Verlag. Stuttgart. 408 pages, 110 figures. DM 55:—.

The diagnostic possibilities in different clotting defects have increased during the past 15 years. The use of new methods of investigation and newly discovered clotting factors have stimulated an intensive study of the clotting mechanism from the biochemical as well as the physiological viewpoint. In spite of this some phases are at present still theories; nevertheless the leading features are known and it is possible, quantitatively, to determine most of the active components. Hitherto it has not been possible to reach a standardized nomenclature but each author has used the one introduced by him, which has made the study of clotting even more difficult.

Prof. Jürgens and doc. Beller have used Koller's nomenclature in their book, but through a detailed table of synonyms it can easily be read by everybody. The book begins with some chapters about the physiology of and a clinic on clotting, wherein there is given an account of our present knowledge of the clotting mechanism. At the same time some of the most disputed questions are illustrated. In these chapters a detailed history is also given, which contributes by giving colour to the book, but is also needed in the description of such a young science, based on many theories. Of the pathologic conditions an account is given both of the congenital and acquired defects, and special interest has been shown both here and elsewhere in the book in the description

and analyses of those conditions appearing because of changed immunological behaviour or the formation of inhibitors. The prime importance of the book lies in the collection of the different methods of analysis, which are of clinical importance. In spite of the tremendous number of analyses which are described there are no difficulties in finding the right one because of the clear organization. This also helps to facilitate the further progress of analysis. The analyses are described in detail after which the method is related in principle. A short chapter is also devoted to the calculating of the clotting factors. There are possibilities to pursue further details through an exhaustive reference list at the end of every chapter, but for clinical and practical use the scope of the book makes it as valuable for the beginner in the clotting field as for the more experienced worker.

Gunilla Berglund, Stockholm

Fred H. Harvie: Pediatric Methods and Standards.

Lea & Febiger, Philadelphia, 1958. 3rd edition. 324 pages, numerous tables. Price \$4.50.

This is a most useful and handy little book that contains a surprisingly large amount of factual data on test methods and methods of treatment, sufficiently detailed to offer real practical help. The size of the volume is small enough to fit into the pocket. The general index, the quality of which is so important for such a book, is sufficiently complete. It will certainly fulfil the purpose set forth by the author, viz., "to be useful for the instruction and orientation of students, and for the everyday care of pediatric patients".

Ph. Bamberger and A. Matthes: Anfänge im Kindesalter.

S. Karger, Basel and New York, 1959. 573 pp., 132 illustrations and 72 tables. Price 80 Swiss francs.

As stated in the foreword, only a few comprehensive studies are available on the

convulsive disorders in childhood. The present study is based on contemporary literature supplemented by the authors' own experiences with some 1600 case histories and 6000 E.E.G. examinations in the Universitäts-Kinderklinik in Heidelberg. The authors address both the practitioners and clinically engaged pediatricians and neurologists.

The greatest space is devoted to the epileptic disorders. It is regrettable that there is no internationally recognized classification system and terminology in this field. To some extent the authors have essayed to create their own classification based on the clinical symptoms. Although one may object to this procedure, it is commendable that mention is also made of synonymous terms used in the literature. An interesting point of view is presented by the introduction of the term "Petit Mal-Trias". In connection with every form of epilepsy, it is amply illustrated by the electroencephalographic relationship. Important contributions are made to the question of the course and prognosis of the disorders. The erethic-hyperkinetic and enechestic syndrome is pointed out as the most obvious psychopathological syndrome in epilepsy in childhood. The pathogenetic relationships are in this respect the subject of a lively discussion. From an etiological point of view it is maintained that in epilepsy we are generally dealing with a causal complex. Most of the manifold imputed etiological factors are discussed. Generally held opinions are expressed on the diagnostic possibilities. The presentation includes the essential features of the anti-epileptic therapy in form of medical, dietetic, and surgical treatments and also in form of psychotherapy. Several very rarely noticed factors of importance are stressed when the question arises about treatment of the acute attack and also concerning the protracted drug treatment.

The febrile convulsions are dealt with extensively. Especially concerning the pathogenesis one encounters essential, unanswered questions and the opinions about the long-term prognosis are highly diverse in the literature. Directions are given for separating

the benign febrile convulsions from those with apparently poorer prognosis. Under the common heading of occasional convulsions (*Gelegenheitskrämpfe*), besides the febrile convulsions there are also discussed post-rachitic tetany, convulsions associated with inflammatory C.N.S. lesions, and convulsions occasionally observed in other diseases such as, for example, pertussis, hemorrhagic diathesis, metabolic disorders, etc. The post-rachitic tetany, spasmophilia, increased in frequency in Germany during the second world war, and thus gave the authors an extensive experience with this nowadays rare entity.

The book ends with a discussion of the respiratory affect-convulsions, syncopic attacks, the rarely seen narcoleptic attacks and hysterical attacks in childhood.

In most chapters the authors present their own catamnestic studies and abundant case descriptions. Some of these exceptional cases might perhaps have been interpreted differently by other clinicians. Essential findings available in the modern literature might have been mentioned, and again some interesting problem situations have not been illuminated. It should also be mentioned that in several instances the text makes reference to authors who are not mentioned in the bibliography. The book is voluminous and comprehensive, but still easily read. This valuable publication is commended both to pediatricians and neurologists.

Bengt Karlsson

Blood Groups.

Brit. Medical Bulletin. Vol. 15. May 1959. The British Council. Davies Street 65. London. 174 pages. Price 20 shillings.

This is a symposium by 19 authors, each prominent in his field of blood research and contains everything worth knowing about blood groups, their clinical importance, inheritance, biochemistry, blood groups and disease, the relation between animal and human blood groups etc. Dr. A. E. Mourant of the Brit. Medical Research Council has

acted as chairman of the Committee preparing the Symposium and Dr. K. L. G. Goldsmith as its Scientific Director. The very rapid progress in blood group research has made it difficult for clinicians to follow its development by studying the current literature and therefore it is a great advantage and very fortunate occurrence to have gotten this excellent summary of the actual knowledge about blood groups.

Recent Advances in Cerebral Palsy, edited by R. S. Illingworth.

J. & A. Churchill Ltd., 104 Gloucester Place, London W.1. 50 sh. net.

Professor R. S. Illingworth, in collaboration with prominent co-workers, has published this monograph on Cerebral Paresis (CP). The work has been anticipated by physicians and others engaged in CP teamwork. Introductorily Illingworth discusses the classification and frequency of CP. He adheres to the division approved by the American Academy of Cerebral Palsy, which is still being criticized, among others by English neurologists. Concerning the frequency of CP Illingworth seems to have arrived at the conclusion that it lies between 1 and 2.1 per 1000 children in England and in Scandinavia, a figure which well agrees with the latest Swedish investigation, 1.6 per 1000 children (M.d'Avignon & L. Gardeström, *Nord. Med.*, 59: 55, 1958). An excellent and well-illustrated chapter on the pathological anatomy is written by C. B. Courville. The important early diagnosis is treated by the senior author. Every possible aspect of the CP therapy is summarily touched upon. The educational problem is extensively discussed. This chapter is written by E. Schonell who stresses among other things the importance of not intermixing in one class CP-children with good intelligence and those with inferior psychic equipment, which must inevitably be the case

when the number of pupils in a CP-school is too small. In other well-written chapters various authors treat of invalid gymnastics, speech therapy, occupational therapy, orthopedic therapeutic methods etc. The book, which is heartily recommended to members of CP-teams, concludes with a chapter on recent developments in brain surgery within this field.

Marcel d'Avignon, Stockholm

Edwin F. Patton: Pediatric Index. A Guide to Symptomatalogical Diagnosis and Current Management.

The C. V. Mosby Co., St. Louis, 1958. Price \$13.50.

Dr. Patton's book represents a new and valuable approach toward the systematization of pediatric knowledge and practice. It is based on authoritative sources from all over the world in conjunction with the author's 35 years of personal experience. The material is very up-to-date and comprehensive in its coverage of the field. The material is arranged in item sections. Section I takes up problems confronting the doctor: complaints, symptoms, signs. These are correlated to three age-groups and their accompanying clinical features. This leads to possible diagnoses which are listed alphabetically. Section II continues with the problem of proving or disproving the probable diagnosis and suggests appropriate therapy. Section III, Special Data and Technique, contains, in alphabetical order, material applicable to severe conditions to save repetition, together with some helpful miscellaneous information. Dr. Patton's book has been in daily use for six months at the hospital and has been found an excellent guide to the practice of pediatrics. It should stand the test of time as a particularly useful aid to general practitioners, students and pediatricians.

John Lind

Studies on Osteopetrosis

II. Investigations Concerning the Nature of the Anaemia

by STIG SJÖLIN

In osteopetrosis the resorption and powers of reconstruction of the newly-formed bone are impaired or lost. The bone-marrow cavity therefore develops abnormally. This defective development of the marrow cavity has generally been held responsible for the extramedullary haematopoiesis and grave anaemia that are encountered in the malignant form of the condition. Four cases of osteopetrosis are now described, special regard being paid to the nature of the anaemia and to the effect of splenectomy. The radiological and histological findings will be reported in a subsequent paper (Part III) by Engfeldt, Fajers, Lodin & Pehrson. Cases 3 and 4 are treated from the genetic point of view in an earlier publication (Part I, by Enell & Pehrson).

Case Reports

In each of the cases described the X-ray appearance of the bones was typical of osteopetrosis. No enlargement of lymph nodes was observed in any of them. The heart and lungs were normal, and no abnormalities were found in the urine or faeces.

Case 1. A.J., a boy born 11/3 1956. The parents were healthy, and as far as was known were not blood relations. There was one healthy brother, born in 1954. There are no known cases of osteopetrosis in the family.

During the period 1/4-26/4 1956 the patient had repeated brief attacks of convulsions, and was admitted to the Paediatric Department of this Hospital on 25th April 1956.

Clinical examination revealed an apparently healthy boy aged 6 weeks (Fig. 1). He measured 55 cm (normal variation 51-60 cm), and weighed 4280 g. He was afebrile, and showed no signs of infection. The liver was palpable 2½ cm below the costal margin, and the spleen 3 cm below. The spleen was strikingly firm to the touch. There was slight exophthalmos. The eye movements were uncoordinated; the right pupil showed a positive consensual light reflex, but did not contract in response to a direct light-stimulus. The right optic disk was pale, but the left was normal. There were no other abnormal neurological signs. The cerebro-spinal fluid was normal, and sub-dural puncture revealed no haemorrhage or effusion.

Laboratory investigations showed the presence of a normochromic anaemia (Hb 10.1 g/100 ml) with marked reticulocytosis (7%) (Fig. 2) and an increase in the number of nucleated red cells (4/100 white cells). Aniso-poikilocytosis and polychromasia were present. No spherocytes were observed. The mean diameter of the red cells was 7.8 μ , and their osmotic and mechanical resistance was normal. The serum iron concentration was 73 μ g/100 ml. There was moderate lymphocytic leukocytosis, with 8% of immature granulocytes. The thrombocyte count was 58,000. A weak, general cold-agglutinin was demonstrated in the serum. Both direct



Fig. 1. Case 1 at 2 months of age.

and indirect Coombs's tests were negative. The fasting blood sugar was 98 mg/100 ml. The serum calcium was 7.3 mg/100 ml, serum phosphorus 4.1 mg/100 ml, and serum alkaline phosphatases 30 Units. The dye test and complement-fixation reaction for toxoplasmosis were negative. The electro-encephalogram was normal.

Course. The convulsions ceased the day after admission to Hospital, and have not recommenced. The serum calcium returned to normal after a few weeks (the boy was given a preparation of vitamins A and D daily from the age of 6 weeks). Air encephalo-

graphy revealed slight distension of the lateral ventricles and slight cortical atrophy. The convulsions were attributed to the hypocalcaemia.

For special reasons the boy remained in Hospital until the age of 13 months. During this period he gained normally in height and weight, and his mental and motoric development were also normal. He cut his first tooth at 5 months, and at 10 months he had 4 teeth in the upper jaw and 2 in the lower. At this time all four upper teeth were extracted owing to caries. While in Hospital he had repeated, brief febrile periods, some for no apparent reason and some due to respiratory infection. Throughout his stay in Hospital he showed a marked tendency to sweating. In the whole, however, his general condition was fair. During the first few weeks after admission the liver and spleen enlarged somewhat; and during the same period the haemoglobin fell further (Fig. 2). The thrombocyte count remained subnormal throughout the time the patient was in Hospital, and on two occasions petechial haemorrhages were observed in the skin. There was leukocytosis (20,000–30,000 c/mm) throughout the whole of this period.

Since the anaemia was partly due to an extracorporeal haemolytic process, splenectomy was carried out at 4 months. The hard, inelastic spleen weighed 125 g. The pathological report is given in Part III. The post-operative course was complicated by infection of the wound, which took one month to heal. The post-operative haemoglobin value and reticulocyte, and thrombocyte counts are shown in Fig. 2. No increased susceptibility to infection was noted following the splenectomy. The appearance of the ocular fundi at 5 months was unchanged.

The patient was still in good condition at 2½ years, but walked only with support and was not talking. The haemoglobin was 11.1 g/100 ml and the reticulocyte count 3%.

Case 2. K.S., a boy born 12/5 1946. The parents were healthy and unrelated. There were no siblings, and there was no known case of osteopetrosis in the family.

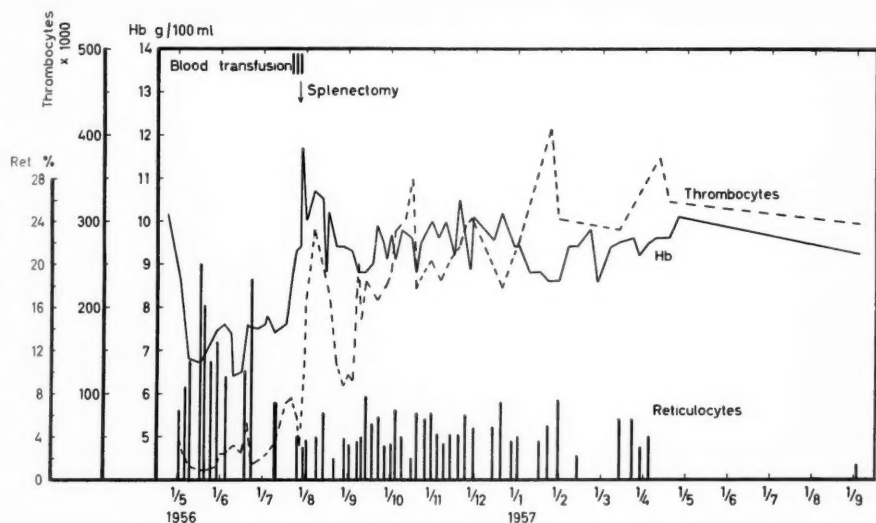


Fig. 2. Case 1. Haemoglobin values and reticulocyte and thrombocyte counts before and after splenectomy.

Anaemia was diagnosed at 2 months of age, blindness at 1 year, and at 7 years ophthalmological examination revealed bilateral atrophy of the optic nerve. Up to the age of one year the child seemed normal: he was able to walk with support, and had cut one tooth. A lateness in development then began to be apparent. He walked unaided at 22 months. He never learned to talk, and his hearing appeared to deteriorate. He cut three more teeth, and all were extracted owing to caries. He remained incontinent of urine and faeces. From the age of 8 years he became increasingly paler and lethargic, and preferred to sit still or lie in bed.

During the period 19/1–12/3 1955 the child was admitted to the Paediatric Department of Gävle Hospital, where the diagnosis of generalized osteopetrosis was established.

He then remained at home until 28/6 1956, when he was admitted to the Paediatric Department of this Hospital owing to progressive deterioration.

Clinical examination revealed an apathetic, lethargic, very pale boy of 10 years (Fig. 3). He was small for his age (114 cm, normal

limits 124–154 cm) and weighed 20.6 kg (normal limits 16.5–23.5 kg). He refused to stand unsupported, and there was genu valga and marked muscular atrophy of the legs. The head was large (circumference 55 cm), with frontal bossing. Nystagmus was present, and the child did not fixate and appeared blind. The pupils were unequal, and did not react to light. The optic disks were pale and atrophic. He did not respond when spoken to, but reacted to loud noise. The audiogram showed response to boneconduction on both sides, up to 65–70 dB. Of the teeth, only a carious remnant of 04 + (Haderup) remained. The liver was only slightly enlarged, but the hard, elastic spleen was palpated 8 cm below the costal margin. Beyond the optic atrophy no neurological signs were detected.

Laboratory investigations revealed marked, normochromic anaemia (Hb 4.4 g/100 ml), with pronounced reticulocytosis (7%) (Fig. 4) and an increase in the number of nucleated red cells (17/100 white cells). There was striking anisocytosis with isolated spherocytes, and poikilocytosis and polychromasia.



Fig. 3. Case 2 at 10 years of age.

The mean red-cell diameter was 7.6μ . The leukocyte count was normal, and the differential count showed the presence of about 15% of immature granulocytes. The thrombocyte count was 47,000. No irregular agglutinins were demonstrable in the serum, and the direct Coombs's test was negative. The serum bilirubin was normal, and the direct

van den Bergh reaction negative. The serum calcium, serum phosphorus, and serum alkaline phosphatase were normal. The erythrocyte sedimentation rate was about 60 mm per hour.

Course. After 3 months' stay in Hospital osteomyelitis of the right maxilla developed. This did not respond to treatment with antibiotics, together with extraction of the one remaining tooth and removal of the surrounding bone.

Since the anaemia was partly of haemolytic nature, splenectomy was performed on 9/1 1957 after repeated blood transfusions. The spleen weighed 540 g, and two walnut-sized accessory spleens were removed at the same time. The pathological report is given in Part III. The blood picture and general condition improved greatly, but the microsedimentation rate did not fall. He was discharged home on 14/2 1957.

In September 1957 osteomyelitis developed in the right mandible. The haemoglobin fell slowly (Fig. 4), but in other respects his condition remained unchanged until 17/1 1958, when sudden deterioration set in, and the patient started vomiting, developed pyrexia and neck rigidity, and became more and more lethargic. He was re-admitted to the Paediatric Department of the University Hospital, Uppsala, on 22/1 1958, in very poor condition, stuporous, with waxy pallor, neck rigidity, and pyrexia. The cerebrospinal fluid was normal. The patient continued to deteriorate, respiration became slow and gasping, and he died on the evening of admission. *Cause of death:* Thrombosis of the right longitudinal sinus and staphylococcal meningitis. The pathologist's report is given in Part III.

Case 3. (described also by Engfeldt, Engström & Zetterström and by Enell & Pehrson), B.J., a girl born 8/7 1949. The family history of this patient is given in Part I.

The diagnosis of osteopetrosis was established at 4 months. The child was subsequently examined at regular intervals at Boden Hospital. Her development was not notably delayed. At 3 years of age optic

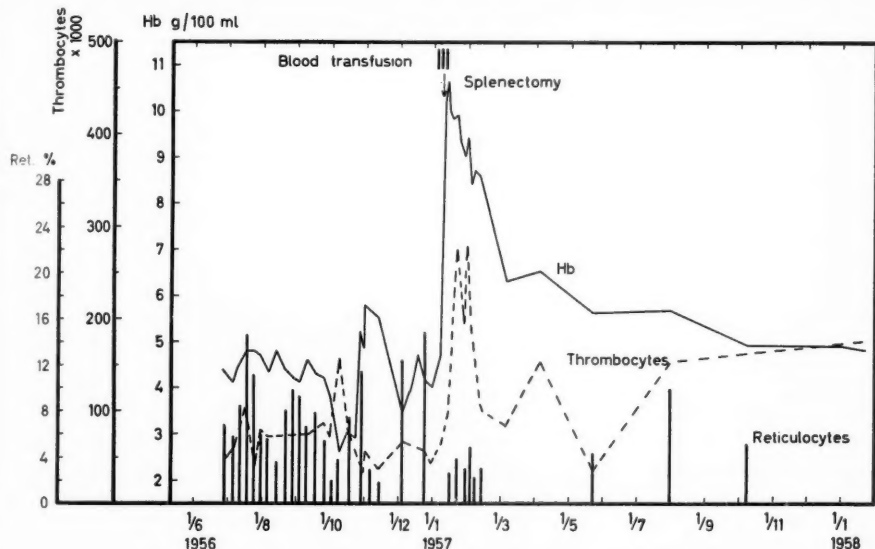


Fig. 4. Case 2. Haemoglobin values and reticulocyte and thrombocyte counts before and after splenectomy.

atrophy, left-sided facial paresis, and slight deafness were diagnosed. During the next few years there was slow deterioration, with increasing impairment of vision, constant nystagmus, progressive anaemia, progressive enlargement of the spleen, repeated epistaxis, and increasing genu valga. She was given many blood transfusions.

The patient was admitted to the Paediatric Department of the University Hospital, Uppsala, on 6/3 1957.

Clinical examination revealed a pale 8-year-old girl in good general condition. She was 114 cm tall (normal limits 113.6–141 cm), and weighed 23.2 kg (normal limits 16.1–23.6 kg). The head was large (circumference 57 cm) with marked frontal bossing. There was genu valga, slight exophthalmos, and optic nystagmus. Examination of the fundi showed pale, atrophic disks. The reactions to light and accommodation were normal. Concerning visual acuity, with the right eye the patient was able to count fingers at a distance of 2–3 metres; on the left side there was nasal hemianopsia. In addition there was

left facial paresis of lower motor neurone type. Audiometry revealed very slight nerve deafness. Of the teeth, only one central upper incisor remained, and a few root remnants and granulomata. The liver was palpable 2–3 cm below the costal margin. The spleen was very firm, and greatly enlarged, and could be felt 10–12 cm below the costal margin. A bony hard tumour the size of a walnut was palpated on the left mandible. The mental development appeared to be normal.

Laboratory investigations showed normochromic anaemia (Hb 7.6 g/100 ml) with marked reticulocytosis (8.6%) (Fig. 5) and an increase in the number of nucleated red cells (17/100 whites). There was anisocytosis, poikilocytosis, and polychromasia, but no typical spherocytes. The osmotic and mechanical resistance of the red cells was normal. There was thrombocytopenia and moderate neutrophil leukocytosis with about 10% immature granulocytes. The micro-sedimentation rate varied between 57 and 27 mm during the first hour.

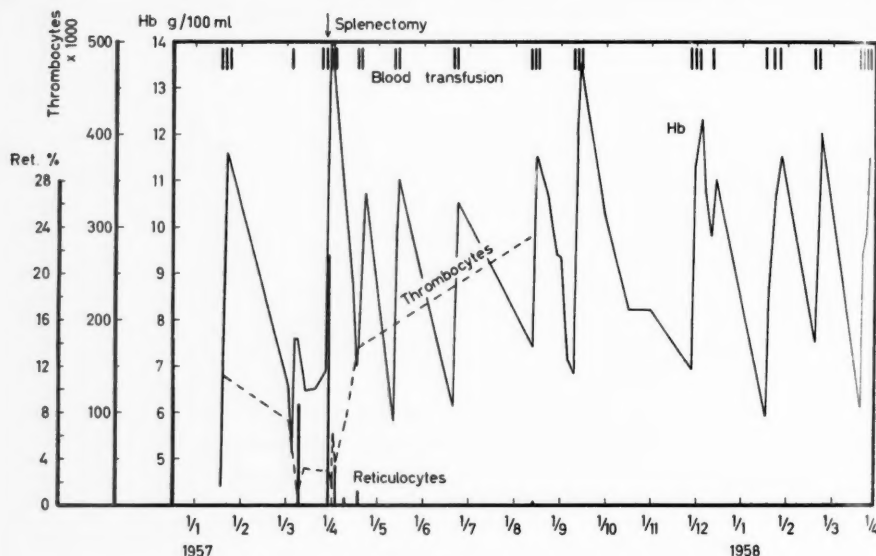


Fig. 5. Case 3. Haemoglobin values and reticulocyte and thrombocyte counts before and after splenoctomy.

Course. As the anaemia was partly haemolytic, splenoctomy was carried out on March 28th 1957. The partially infarcted spleen weighed 600 g. At the hilum there were several accessory spleens, which were also removed. Liver puncture was performed (for pathological report see Part III). The post-operative course was uneventful, and the patient was discharged home on April 10th 1957, since then she has been repeatedly examined at the Paediatric Department of Boden Hospital. The gradual deterioration has continued, and the anaemia has required repeated blood transfusions (Fig. 5).

Case 4. (also described by Enell & Pehrson), A.M.Ö., a girl born 21/3 1946. For the family history see Part I.

After the age of 6 months the infant was noticed to be becoming increasingly pale. She was admitted to the Paediatric Department of Boden Hospital for the first time at 15 months, and was found to have changes typical of osteopetrosis. The motorial deve-

lopment was slightly delayed, but mental development has been normal.

To start with, the development of the teeth was normal, but the child has subsequently lost all her teeth. The optic disks grew progressively paler, and at 6 years the right eye was almost blind, whereas vision on the left side was good. The anaemia has progressed slowly, and at 6 years of age she has received numerous blood transfusions. At the same time the spleen has grown in size, and finally became distressingly heavy.

The child was admitted to the Paediatric Department, University Hospital, Uppsala on April 28th 1958.

Physical examination revealed a pale 12-year-old girl whose general condition was good. The height was 123 cm (normal limits 130.9–166.9 cm) and the weight 26 kg (normal limits 18.5–28.6 kg). The head was large (circumference 56 cm), with prominent frontal bossing, and there was genu valgum, exophthalmos, and right-sided divergent strabismus. The pupils responded normally

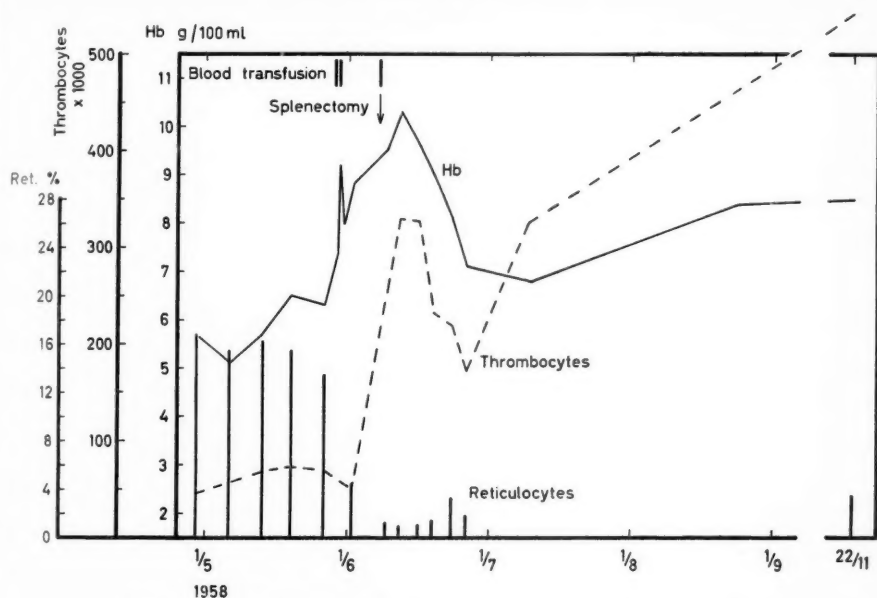


Fig. 6. Case 4. Haemoglobin values and reticulocyte and thrombocyte counts before and after splenectomy.

on both sides. Tests of visual acuity revealed on the right side perception and localization in the upper fields only, and on the left side 0.9-1.0 uncorrected. Both optic disks were atrophic and pale. Audiometry revealed bilateral impairment of conduction (40 dB right ear, 50 dB left ear). The liver was palpable 2-3 cm below the costal margin. The spleen was firm and greatly enlarged, reaching the iliac crest on the left and the mamillary line down into the iliac fossa on the right.

Laboratory tests showed normochromic anaemia (Hb 5.7 g/100 ml) with marked reticulocytosis (16.8%) (Fig. 6) and an increase in the number of nucleated red cells (10-100 whites). There was anis- and poikilocytosis and polychromasia, but no spherocytes. The osmotic and mechanical resistance of the red cells was normal. The thrombocyte count was 45,000. The total leukocyte count was normal, and the proportion of immature granulocytes about 5%. Coombs's direct test was negative. The serum iron concentration

was 144 μ g/100 ml, and the total ironbinding capacity 465 μ g/100 ml. The serum bilirubin concentration was 3.0 mg/100 ml. The microsedimentation rate was 50 mm during the first hour. The serum calcium, serum phosphorus, and serum alkaline phosphatase were normal. Leno-portal venography revealed strikingly wide splenic and portal veins, and the intrahepatic branches of the portal vein were normal. No collaterals were seen.

Course. Since the anaemia was partly haemolytic in nature, and owing to the immensity of the spleen, which caused the patient considerable distress, splenectomy was carried out on June 4th 1958. The spleen weighed 1150 g. (For pathological report, see Part III.) At the hilum there were 3 accessory spleens, which were also removed. One accessory spleen near the pancreas was left. The liver was normal in size and appearance. Biopsy of the liver was carried out. (For report, see Part III.) The postoperative course was uneventful, and the child was discharged home on June 26th 1958. Her

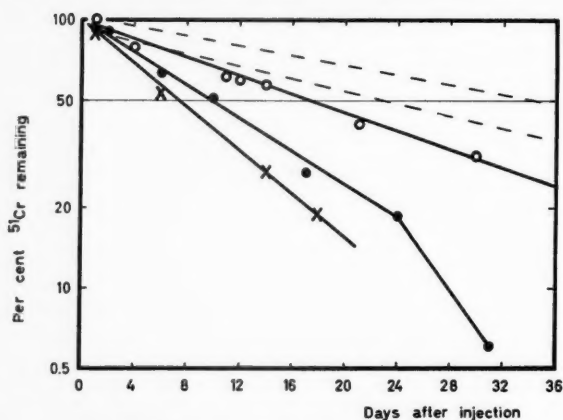


Fig. 7. *Case 1.* Survival of the patient's Cr^{51} labelled red cells after autotransfusion before splenectomy (●—●), and survival of Cr^{51} -labelled red cells from a healthy adult after transfusion to the patient before (x—x) and 2 months after (○—○) splenectomy. The interrupted lines indicate the normal variation (± 2 SD) in 12 male adults.

general condition has remained good, and since the operation she has felt very much better. The effect on the haemoglobin, reticulocyte, and thrombocyte figures is apparent from Fig. 6.

Special Haematological Investigations

Since a haemolytic process is the commonest cause of marked reticulocytosis such as was found in these 4 cases of osteopetrosis, the life-span of the red blood cells was estimated by labelling them in vitro with radio-active chromium (Cr^{51}), as described by Gray & Sterling (1950). The activity in blood samples taken 20–30 minutes after injection of the Cr^{51} was taken as 100%. Survival curves after autotransfusion of red cells in 12 healthy male adults revealed a mean apparent half-life of 27.5 days ($\text{SD} = \pm 2.25$ days).

In Cases 1, 3 and 4 the red cell survival was studied after autotransfusion. A considerably reduced survival period was noticed in all of them, the apparent half-

times being 10, 9.5, and 9 days (Figs. 7 and 9).

To determine whether the shortened life-span of the red cells in osteopetrosis is due to an extra- or intracorporeal factor, further transfusion experiments were done. Red cells tagged with Cr^{51} from 2 healthy adults were injected into 2 of the patients, Cases 1 and 2. In both experiments the donor's and recipient's cells were similar with respect to ABO and D factors in the Rh system. Cross-matching in salt medium and Coombs's indirect test were negative. In both cases the erythrocytes showed shortened survival times, with apparent half-times of 7.5 and 7 days respectively (Figs. 7 and 8). Erythrocytes from Case no. 4 (Blood Group 0 Rh+) were tagged with Cr^{51} , and injected into 2 healthy adult recipients, one belonging to Blood Group 0 Rh+ and the other to A Rh+. Both cross-matching and Coombs's indirect test were negative. In both cases entirely normal

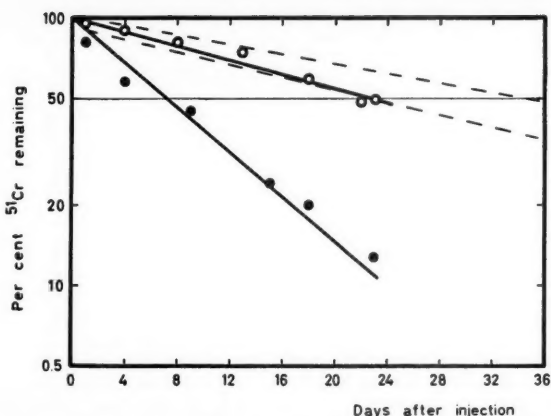


Fig. 8. Case 2. Survival of Cr^{51} -labelled red cells from an adult after transfusion to the patient before (●—●) and 3 weeks after (○—○) splenectomy. The interrupted lines indicate the normal variation (± 2 SD) in 12 male adults.

survival curves were obtained (apparent half-times 22 and 32 days, respectively). It may therefore be considered certain that the haemolytic process in osteopetrosis is entirely extracorporeal in nature.

The combination of extracorporeal haemolytic anaemia, thrombocytopenia,

and splenomegaly without demonstrable circulating antibodies provides strong evidence of splenic hyperfunction as the cause of both the haemolytic anaemia and the thrombocytopenia. For this reason splenectomy was carried out in all 4 cases. In Cases 1, 2, and 4 the life-span of the red

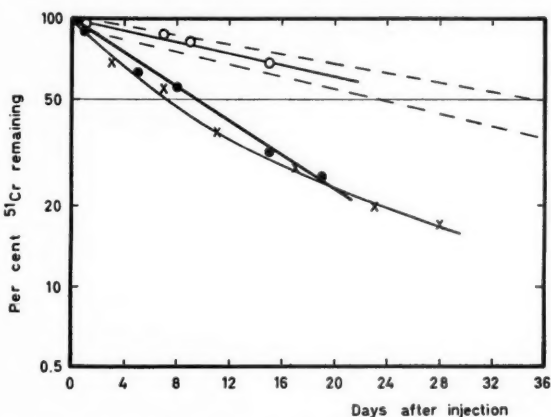


Fig. 9. Case 3. Survival of the patient's Cr^{51} -labelled red cells after autotransfusion before splenectomy (●—●). Case 4. Survival of the patient's Cr^{51} -labelled red cells after autotransfusion before splenectomy (x—x). Survival of Cr^{51} -labelled red cells from a healthy adult after transfusion to the patient 1 week after splenectomy (○—○). The interrupted lines indicate the normal variation (± 2 SD) in 12 male adults.

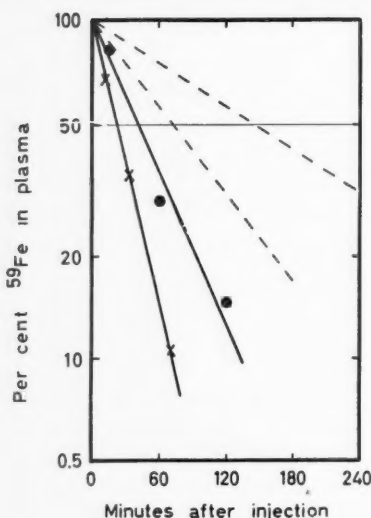


Fig. 10. Concentration of Fe^{59} in plasma after intravenous injection, in Cases 1 (●—●) and 4 (x—x). The interrupted lines show the normal variations according to Wasserman *et al.*

cells was again estimated after operation. Red cells from healthy donors were used. In Cases 2 and 4 normal survival curves were obtained (Figs. 8 and 9). In Case 1 the survival time had improved, but was not completely normal (apparent half-time 17.5 days) (Fig. 7).

In Cases 1, 2, and 4 investigations into the iron-metabolism were carried out before splenectomy, with the aid of radioactive iron (Fe^{59}) injected intravenously as described by Huff, Hennessy, Austin, Garcia, Roberts & Lawrence. Fe^{59} disappeared from the plasma at an increased rate in Cases 1 and 4 (Fig. 10). (In Case 2 the plasma disappearance was not studied.) The rate at which Fe^{59} was incorporated into the circulating red cells was normal; but only 35–52 % of the dose administered was recovered from the red

cells, compared with 75–90 % normally (Fig. 11). Further, the radio-activity was found to disappear from the circulating blood at an abnormally fast rate (Fig. 11). In Cases 2 and 4 the uptake of Fe^{59} in the bone-marrow, liver, and spleen was also traced, by means of external measurements of radio-activity over the organ in question, as described by Elmlinger, Huff, Tobias & Lawrence. The characteristic divergencies from the findings in a healthy adult are evident from Fig. 12. In both cases of osteopetrosis the highest activity was throughout noted over the spleen, the next highest over the liver, and the lowest over the bone-marrow. In healthy

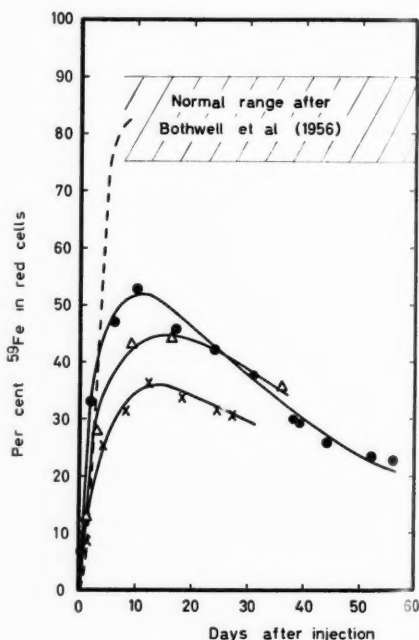


Fig. 11. Concentration of Fe^{59} in the circulating red cells after intravenous injection in Cases 1 (●—●), 2 (△—△) and 4 (x—x). The interrupted line indicates the normal uptake, and the hatched area indicates the normal variations according to Bothwell *et al.*

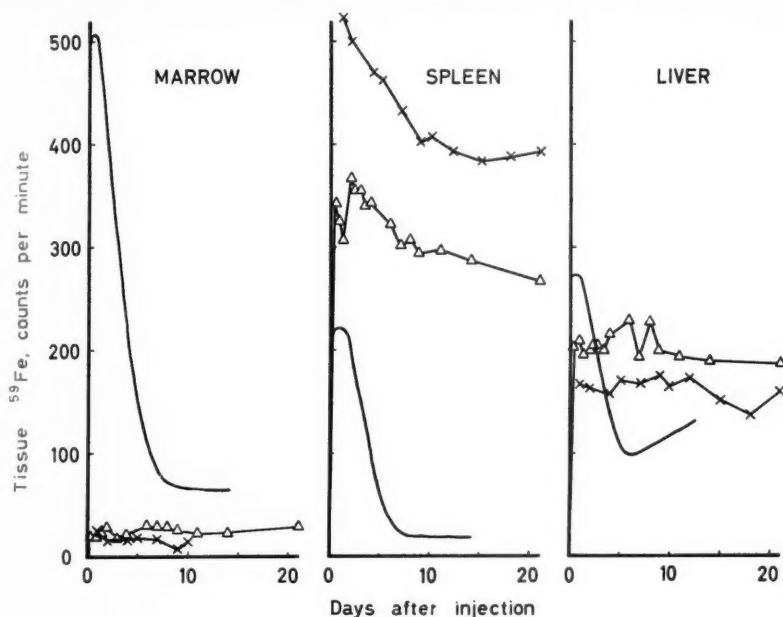


Fig. 12. Radio-activity over bone-marrow, liver, and spleen after intravenous injection of Fe^{59} in Cases 2 (Δ) and 4 (\times). The smooth curves show the findings in a healthy adult (after Fabi *et al.*).

persons the opposite is true, the highest activity being found over the bone-marrow and the lowest over the spleen. And the radio-activity diminished considerably more slowly over the liver and spleen in the two child patients than in a healthy adult.

To exclude the presence of intestinal haemorrhage the faecal content of Cr^{51} and Fe^{59} was measured over 3 days in Cases 1 and 4. Of the dose administered, 0.1 % of Cr^{51} and 0.08 % of Fe^{59} were excreted per day in Case 1, which corresponds to 0.09 and 0.05 ml of red cells. In Case 4 0.15 % of Cr^{51} was excreted per day, but no Fe^{59} activity could be demonstrated, and intestinal bleeding is

therefore also excluded in this case. Weber tests repeated at regular intervals were also negative in all 4 cases.

Discussion

The anaemia of osteopetrosis has in the past largely been ascribed to encroachment by the diseased medullary bone upon the space that is normally available for blood-formation in the bone marrow (cf. Fairbank; Kneale & Sante). This belief has been compatible with the concomitant, often marked extramedullary erythropoiesis. Since the anaemia has not always followed exactly the degree of radiological opacity of the diaphyses, however, other theories have been put forwards. Thus,

McCune & Bradley have suggested the possibility of a primary defect of the bone marrow. Van Creveld & Heybroek have raised the question of whether both the bone-lesions and the anaemia may not be due to a primary developmental mesenchymal disturbance or degeneration. None of these authors have been able to provide any evidence to support their theories, however.

In view of the uncertainty concerning the true nature of the anaemia, it is surprising how little attention has been paid to the fact that the blood picture in osteopetrosis is characterized not only by anaemia but also by the presence of numerous nucleated red cells, and in cases subjected to thorough haematological investigation, pronounced reticulocytosis. The combination of anaemia and reticulocytosis would first and foremost indicate a haemolytic syndrome, and the nonparallelism of the degree of anaemia and the roentgen appearance of the bone might therefore be suspected to be due to a haemolytic factor.

The first to entertain doubts on this matter seems to have been Frank (1931), who also carried out splenectomy on a 3-month-old boy with typical osteopetrosis. In this case operation was without marked effect. Subsequently, Lefebvre, Vandendrop & Benoit have reported the case of an 11-month-old girl with osteopetrosis and clinical signs of haemolytic anaemia, in whom the anaemia was interpreted as being due to hypersplenism and splenectomy was performed. The effect upon the general condition and blood picture was strikingly good. In 1955, after having found a high endogenous production of carbon monoxide in a case of

osteopetrosis, Engfeldt, Karlberg & Zetterström concluded that haemolytic anaemia was present. In 1957 Zetterström demonstrated hyperhaemolysis in another case of osteopetrosis: after tagging with Cr^{51} and auto-transfusion "a mean survival-time of 35-40 days" was shown by the red cells.

In the present investigation the red cells from 4 cases of osteopetrosis have shown a greatly diminished survival-time, and the haemolytic process has been shown to be entirely extracorporeal in nature. Since no circulating antibodies could be demonstrated, and since in 3 cases the life-span of the red cells was prolonged after splenectomy, it may furthermore be considered established that the hyperhaemolysis in these cases was wholly or partly due to hypersplenism.

Despite the clear indication for splenectomy that hypersplenism is considered to constitute, the clinical effect of removal of the spleen was not entirely unequivocal. A marked, prolonged remission was obtained in Case 1. The haemoglobin value improved, the reticulocytosis diminished, and the thrombocyte count returned to normal (Fig. 2). This remission may reasonably be ascribed to the splenectomy. It should however be noted that the life-span of the red cells did not become completely normal, and that slight anaemia persisted even after operation. In Case 2, there was improvement, with higher haemoglobin values, diminished reticulocytosis, and a raised number of thrombocytes (Fig. 4), but part of the effect proved to be only temporary: the haemoglobin fell slowly, and 8-9 months after splenectomy it had again reached the pre-operation level. In Case 3 the effect of splenectomy

is assessed with some difficulty owing to the energetic, systematic transfusion therapy that was instituted as early as 3 weeks after operation (Fig. 5). At that time, however, the haemoglobin level was as low as 7 g/100 ml and the effect upon the anaemia must in any event be regarded as doubtful. On the other hand, the thrombocytopenia seemed to have been corrected by the procedure even in this case. In Case 4 there was an increase in the haemoglobin, the reticulocyte count fell considerably, and the thrombocyte count was restored to normal (Fig. 6).

The inconstant effect of splenectomy upon the anaemias indicates that factors over and above hypersplenism must exert an influence on the anaemia of osteopetrosis. In attempts at elucidating this problem, attention is directed in the first place towards the magnitude of the compensatory erythropoiesis of the spleen. Histologically the splenic erythropoiesis was moderate to lively, and probably more active than that in the liver (see Part III). Some idea of the blood-forming capacity of the spleen may probably also be obtained from the investigations into the uptake of radio-active iron by different organs. In Cases 2 and 4 the greatest radio-activity was recorded over the spleen, the next greatest over the liver, and the least over the bone marrow (Fig. 12). In healthy subjects the opposite is true, with the greatest activity over the bone marrow and the least over the spleen. The interpretation of these findings is not altogether clear. In general the process of distribution of the radio-active iron between these organs is taken as mainly conditioned by the degree of erythropoiesis in them. There are two other fac-

tors in cases of osteopetrosis that greatly affect the amount of radio-active iron taken up by the spleen and render difficult the evaluation of the measurements. Firstly, there is with all probability increased blood flow owing to splenomegaly and secondly, there was considerable hyperhaemolysis in the spleen. Both of these factors ought reasonably to bring about an increase in radio-iron-activity in the organ. The investigations carried out do not provide any means of assessing the mutual significance of the three factors, but it would seem likely to assume that fairly considerable new formation of erythrocytes is taking place in the spleen. The fact that the anaemia was never fully corrected by splenectomy might be explained by the loss of the blood-forming tissue of the spleen. There is also another factor that may have contributed to this phenomenon, namely that it is possible that not only the spleen but also other parts of the reticulo-endothelial system may be capable of haemolytic activity sufficient to prevent complete correction of the anaemia. This could explain the failure in Case 1 of the survival-time of the red blood cells to return to normal after splenectomy, and also the residual reticulocytosis. The fact that the reticulocytosis persisted after splenectomy in Cases 2 and 4 also, even though the survival time of the red cells had become normal may appear difficult to explain. It is possible that the reticulocytosis in these two cases is connected with the fact that the erythropoiesis is taken place outside the medulla. The explanation would be that the red cells thus formed pass into the circulation at an earlier stage of maturity than red cells formed in the bone marrow.

From the above it should be clear that splenectomy is not necessarily indicated in the anaemia that accompanies osteopetrosis, but it is evident from the good effect upon the anaemia in 2 of the 4 cases and from the improvement in the thrombocytopenia in all 4 cases that it may be worth considering in certain cases. It is possible that simultaneous study of the distribution of radio-active iron and chromium between the organs concerned may give information about the erythropoietic activity and the degree of hyperhaemolysis such as to facilitate selection of cases for splenectomy.

It is at present hardly possible to interpret all details of the results of the experiments with radio-active iron. The rapid disappearance of this substance from the plasma may very well be explained by the increased erythropoiesis that always accompanies haemolytic anaemia. Similarly, the small uptake of radio-active iron by the circulating red cells fits in with the findings in other haemolytic anaemias. The fact that the concentration of radio-active iron in the red cells begins to fall after as little as 10–20 days means that the radio-iron from haemolysed red cells is not re-utilized as quickly as normal for erythropoiesis. A fall such as this might be due to simultaneous haemorrhage, but since none could be demonstrated the explanation must be that some of the radio-active iron liberated during the haemolysis is re-directed to certain iron depots with a comparatively slow turnover. The investigations into the distribution of radio-active iron between various organs, from which it is clear that the radio-activity over the spleen and liver fall considerably more slowly than in healthy

subjects, support this view (see Fig. 12). This could be explained by the presence of large, stable stores of iron in liver and spleen. The histological investigations, which revealed a fairly abundant amount of haemosiderin in the spleen, also bears out this theory.

Finally, the degree to which blood transfusion is justified in treatment of the anaemia of osteopetrosis will be briefly discussed. Having regard to the increasing risk of immunization involved by every new blood transfusion, the greatest restrictiveness should in general be exercised. Furthermore, blood transfusion always produces some inhibition of spontaneous erythropoiesis, which readily leads to vicious circle in which each transfusion automatically actuates another. And it should be borne in mind that these patients often do remarkably well even with low haemoglobin values.

Summary

The cases of 4 children with malignant osteopetrosis are discussed with special regard to the haematological findings. Investigations showed that the anaemia was essentially due to an extracorporeal haemolytic process, with all probability due to hypersplenism. Since the effect of splenectomy was not entirely equivocal, other factors are discussed, including loss of splenic haematopoiesis, and general hyperactivity of the reticulo-endothelial system, that may be contributory to the anaemia that persisted after splenectomy. That hypersplenism existed is also illustrated by the fact that the thrombocytopenia that was present in all cases was corrected by the splenectomy. The

indications for splenectomy and blood transfusion in osteopetrosis are discussed in the light of the 4 cases described. Investigations into the iron metabolism with the aid of Fe^{59} showed that the iron that is liberated on haemolysis of the red cells is not re-utilized in erythropoiesis as quickly as is normally the case; the haemoglobin iron is probably directed in the first place

to iron stores with a relatively slow turnover.

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Etudes sur l'ostéopétrose. II. Recherches sur la nature de l'anémie

Discussion sur les cas de quatre enfants atteints d'ostéopétrose maligne. Dans cette discussion on considère particulièrement les découvertes hématologiques. Des recherches ont montré que l'anémie était essentiellement due à un processus hémolytique extracorporel dû probablement à une hypersplénie. L'effet d'une splénectomie n'étant pas tout à fait incertain d'autres facteurs sont discutés y compris la perte de l'hématopoïèse de la rate et l'hyperactivité générale du système réticulo-endothélial, qui pourraient contribuer à l'anémie qui persista après la splénectomie. L'existence d'une hypersplénie est aussi démontrée par le fait que la thrombocytopénie existante chez les quatre cas fut corrigée par la splénectomie. Les indications pour splénectomie et transfusion de sang en cas d'ostéopétrose sont discutées à la lumière des quatre cas décrits. Des recherches dans le métabolisme du fer à l'aide de Fe^{59} montrent que le fer libéré par hémolyse des cellules rouges n'est pas réutilisé en érythropoïèse aussi rapidement que la normale; le fer de l'hémoglobine est probablement dirigé d'abord vers des dépôts de fer avec une réutilisation relativement lente.

Studien zur Osteopetrose. II. Untersuchungen über die Natur der Anämie

Es werden die Fälle von 4 an maligner Osteopetrose leidenden Kindern diskutiert, wobei besonders auf die hämatologischen Befunde eingegangen wird. Die Untersuchungen zeigten, daß die Anämie im wesentlichen auf einem extrakorporellen hämolytischen Prozeß beruhte, der aller Wahrscheinlichkeit nach auf eine Hypersplenie zurückzuführen ist. Da die Auswirkungen der Splenektomie nicht vollkommen eindeutig waren, werden noch andere Faktoren diskutiert, einschl. Verlust der Milzhämatopoese und allgemeine Überfunktion des retikuloendothelialen Systems, die eventuell zu der nach der

Splenektomie andauernden Anämie beitragen. Daß eine Hypersplenie bestand, wird auch noch durch die Tatsache veranschaulicht, daß die in allen Fällen existierende Thrombozytopenie durch die Splenektomie behoben wurde. Die Indikation für eine Milzexstirpation und Bluttransfusion bei Osteopetrosis wird an Hand der 4 beschriebenen Fällen diskutiert. Untersuchungen des Eisenstoffwechsels mit Hilfe von Fe^{59} zeigten, daß das bei der Hämolyse der roten Blutkörperchen freiwerdende Eisen für die Erythropoese nicht so schnell wieder verwertet wird, wie es allgemein der Fall ist; das Hämoglobineisen wird vermutlich zuerst zu Eisendepots mit einem relativ langsamen Umsatz geleitet.

Estudios sobre osteopetrosis. II. Investigaciones relativas a la naturaleza de la anemia

Se discuten los casos de 4 niños afectados de osteopetrosis, haciendo referencia especial a los hallazgos hematológicos. Las investigaciones mostraron que la anemia se debía esencialmente a un proceso hemolítico extracorporeal, con toda probabilidad debido a hipersplenismo. Como quiera que el efecto de la esplenectomía no era enteramente inequívoco, se discuten también otros factores, incluyendo la pérdida de la hematopoyesis esplénica y la hiperactividad general del sistema reticuloendotelial que podrían contribuir, eventualmente, a la anemia subsistente después de la esplenectomía. La existencia de hipersplenismo es confirmada también por el hecho de que la trombocitopenia, presente en todos los casos, fue corregida por la esplenectomía. Las indicaciones para una esplenectomía y transfusión de sangre en la osteopetrosis se discuten a la luz de los 4 casos descritos. Ciertas investigaciones del ferrometabolismo, realizadas con auxilio del Fe^{59} , mostraron que el hierro liberado en la hemólisis de los eritrocitos no vuelve a utilizarse en la eritropoyesis tan rápidamente como ocurre normalmente; el hierro de la hemoglobina es dirigido, probablemente, en primer lugar a depósitos con una reutilización relativamente lenta.

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Department of Paediatrics
University Hospital
Uppsala
Sweden

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From the Department of Paediatrics, Karolinska Sjukhuset, Stockholm, Sweden

Roentgenological Considerations of Upper Gastro-Intestinal Bleeding and Peptic Ulcer in Children

by PEKKA SOILA¹

Recognition of the safety and diagnostic gains attributable to an early roentgen examination in haematemesis and/or melæna and the desirability of an accurate diagnosis in often critically ill children have given rise to the present analysis. Special attention will be paid both to the reliability of the roentgen examination, and to the incidence of peptic ulcer and its significance as a source of bleeding.

Case reports and comments upon various aspects of the problem have been published from many countries. In 1941 Bird *et al.* collected 243 cases from the literature adding one case of their own and discussed the surgery of peptic ulcer in paediatric patients thoroughly. Since World War II a number of reports have been published (1, 4, 13, 16, 20, 25, 26, 28, 31, 33, 38, 45, 48). Sometimes the role of roentgen examination is emphasized. At times the diagnosis was not made until autopsy. The latter situation occurs particularly in infants, who can be examined only with difficulty. An interesting case of bleeding duodenal ulcers involving infant twins with liver damage was reported by Kempton & Bodian (24). Children of preschool-age have been considered as a group by Goldsberry (18), those of school-age by Dubarry (11), Forssell (15) and by Karlström (23).

Other sources of bleeding can be mucosal changes or état mammelonné; (Walk, 46), oesophageal ulcer (Marguézy & Royer, 32), oesophageal varices either congenital or secondary (Jorup, 22) and diaphragmatic hernia (Gross, 19). Schneegans *et al.* (40) have reported pyloric spasm as a cause of bleeding.

The reports published almost invariably emphasize the importance of accurate diagnosis and treatment of bleeding patients. In addition they assume the number of cases to be more frequent than is usually recognized. The more sizable materials published throw some light on these aspects. Thus Karlström reports duodenal ulcer in 17 boys and 7 girls, gastric ulcer in 3 boys and 3 girls. Brayton & Norris (8) had 31 cases of upper gastro-intestinal bleeding, among them 17 cases of oesophageal varices. Lusztig *et al.* (29) found 23 ulcers in 1745 autopsies, of which 10 resulted in bleeding. Benner (5) reports duodenal ulcers in 1.4% of 500 autopsies.

The relevant roentgenological problems have been discussed by Alexander (2), Aye (3), Canestri (9), and Morgan (34).

Material and Methods

Twenty-six patients with upper gastro-intestinal bleeding and/or peptic ulcer have been treated in the Dept. of Paediatrics, Karolinska Sjukhuset, since its opening

¹ James Picker Foundation Research Fellow.

TABLE 1. *The age distribution of the patients and the types of examinations performed (oesophagus-stomach-passage-scout film of the abdomen).*

	< 1 y.	1-6 y.	7-10 y.	11-14 y.	Total
BOYS					
4 (----)		2 (1-2-1-2)	3 (2-3-3-2)	7 (0-7-0-0)	16 (3-12-4-4)
GIRLS					
5 (1-1-0-1)		4 (4-2-1-3)	1 (0-1-0-0)	— (----)	10 (5-4-1-4)
TOTAL					
9 (1-1-0-1)		6 (5-4-2-5)	4 (2-4-3-2)	7 (0-7-0-0)	26 (8-16-5-8)

July 1, 1951 until Oct. 31, 1958. Sixteen boys and ten girls were involved, with the age distribution shown in Table 1, in which are also listed the types of roentgen examinations. During the investigation uniform criteria in selecting the material were employed, viz. a definite history of large, often repeated haematemeses, blood in faeces verified by a positive Weber test, and anaemia with the number of erythrocytes reduced to 3.5 million or less. In the case of the newborn there might be some difficulty in evaluation, but these patients were as a rule admitted directly from the maternity ward. Ulcer patients were accepted according to known criteria.

During the same time period, a total of some 23,000 patients have been treated in the course of some 29,600 admissions. The relevant roentgen examinations total 1221, subdivided into 359 examinations of the oesophagus, 792 of the stomach and 70 of the small bowel.

The patients were subjected to roentgenological examination irrespective of the severity of their illness. No complications arose from stomach examinations and it was also found that examinations of the oesophagus and the small intestines constitute no additional hazards. The exposures were quite numerous comprising mucosal and filling pictures of the oesophagus and stomach in various projections; the former being reproduced in at least 6-8 exposures, the latter never in less than 10, frequently in more than 20 exposures. The patients were ex-

amined in the upright position provided that they could sufficiently cooperate and the examination was completed in recumbent positions. The fluoroscopy and filming were performed by the residents, the final interpretation was made by a staff radiologist in cooperation with the fluoroscopist.

Evaluation of the Roentgen Findings

The roentgenological changes pertinent to the problem are fairly well known. However, the small size of the patients and the relative rarity of these cases individualize the lesions and the findings to a considerable extent and imply the need for great care during fluoroscopy and interpretation. Thus duodenal ulcer may be of the acute variety without deformation of the duodenal cap and changing degrees of compression should be applied for its proper demonstration. Exposures in various projections and various contraction phases are of importance. Though most cases of duodenal ulcer in children show a chronic course of the disease, the possibility of a transient lesion cannot be excluded.

More frequently, however, a grossly deformed first portion of the duodenum is found. Fig. 1 illustrates a case who had been



Fig. 1.

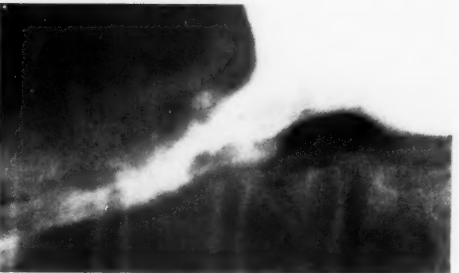
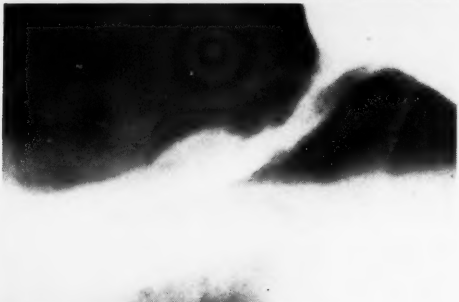


Fig. 3.

Fig. 1. Grossly deformed first portion of duodenum in a bleeding patient. A large ulcer crater was demonstrated and verified at operation.
 Fig. 3. Oesophageal ulcer and short oesophagus in a patient with Moncrieff's syndrome. At operation oesophagitis and a callous ulcer were found.

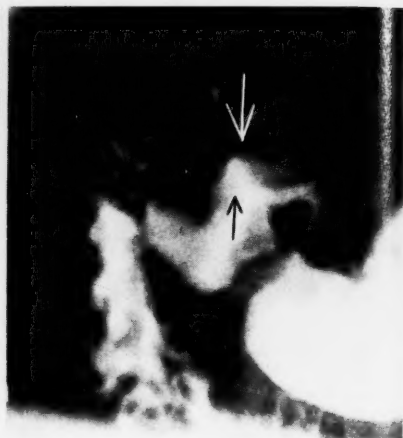


Fig. 2. Duodenal ulcer with haemorrhage in a 12-year-old boy. The patient had been hospitalized at the age of five because of bleeding; no roentgen examination at that time.

bleeding, vomiting blood for several days, and continued to bleed after admission, until resected. A large niche can be discerned in the radiographs, a frequent feature of bleeding, chronic, grossly deformed duodenal cap. Fig. 2 shows the duodenal bulb and ulcer of a 12-year-old boy vomiting blood. This boy had been hospitalized at the age of 5 because of haematemesis and anaemia with a Hb 7.5%, and R.B.C. 2.6 millions. At that time no roentgen examination of the gastro-intestinal tract was done. In all probability the cause of the bleeding was even then a duodenal ulcer. This case emphasizes the importance of roentgen examination in all age groups, provided that the patient's general condition permits full manipulation yielding adequate results.

Fig. 3 shows the only oesophageal ulcer combined with a hiatus hernia found in the present series. This patient also had sucrose-uria and idiocy (Monierieff's syndrome) and was a difficult subject to examine. The ulcer was visible on a few films at the fifth examination. Previously some mucosal disturbance of the lower oesophagus had been found. At operation according to Allison a callous oesophageal ulcer was resected.

The recognition of mucosal changes as a source of diffuse bleedings constitutes a dif-

ficult problem from the roentgenological point of view. Besides the possible comparative studies including gastroscopy, surgical and microscopic specimens, the functional characteristics revealed at roentgen examination are of importance. Fig. 4 shows the duodenal bulb of a patient with haematemesis. There is some radiation of the mucosal rugae but no definite niche, oedema of the wall, or deformation.

Sometimes extensive lesions may involve the gastric mucosa, as illustrated by Fig. 5. The coarse and hypertrophic mucosal pattern was suspected as a source of bleeding in a 5-year-old boy. Gastroscopy and subsequent operation revealed teleangiectasia of the gastric wall, exempting only the pyloric region.

Results

The 26 patients with upper gastrointestinal bleeding and/or peptic ulcer out of 23,000 patients constitute an incidence of approximately 1:1000. There were 22 patients bleeding, and 4 patients revealing an ulcer without evidence of haemorrhage. Eighteen patients were subjected to roent-



Fig. 4.



Fig. 5.

Fig. 4. Deep mucosal folds visible in extreme second oblique projection (c), but not in numerous other films taken in other projections and various contraction phases (a-b).

Fig. 5. Telangiectasiae involving corpus and fundus of the stomach (a). The same after air-insufflation (b). Note the rather more regular mucosal pattern in the prepyloric portion (c-d).

TABLE 2. *Results.*

1: Total 26 patients. 2: 18 roentgen examined. 3: 14 bleeding. 4: 11 peptic ulcers (7 bleeding).

< 1 y.	1-6 y.	7-10 y.	11-14 y.
BOYS			
4 no exam. 4	2 Teleangiect. ventr. 1	3 ulcer duodeni 1	7 ulcer duodeni 7
bleeding 4	bleeding 1	bleeding —	bleeding 3
	nil 1	ulcus ventr. 1	
	bleeding 1	bleeding 1	
		ulcus oesophagi 1	
		bleeding 1	
GIRLS			
5 no exam. 4 ^a	4 nil 4	1 ulcer ventr. 1	—
bleeding 4	bleeding 4	bleeding 1	
nil 1			
bleeding 1			

^a One autopsied patient had been bleeding from the oesophageal mucosa.

gen examination, the omitted 4 boys and 4 girls all belonging to the infant group.

The 18 examined patients comprise 12 boys and 6 girls. Eleven revealed a peptic ulcer, there being 8 duodenal ulcers, 2 gastric ulcers and one oesophageal ulcer. One girl had a gastric ulcer, all other ulcer patients (10:1) were boys. The two gastric ulcer patients were followed until the crater was no longer demonstrable. One duodenal ulcer patient had no clinical recurrence, all other duodenal ulcer patients showed a rather chronic course of their illness. It is remarkable that bleeding complicated 7 of the 11 peptic ulcer cases. The 7 cases without peptic ulcer all had bleeding, and the total of roentgen-examined bleeders thus is 14 cases.

One of the last-mentioned 7 cases was diagnosed as teleangiectasiae of the stomach (published by Ehrenborg *et al.*, 12). One patient had been examined and treated for many years for his bleeding, and had undergone an abdominal operation,

but without any conclusive diagnosis. Five patients showed a transient course of the bleeding episode without roentgenological evidence of the lesion. Thus two thirds of the examined total and a good half (8:14) of the examined bleeders could be provided with a roentgenological explanation of their condition.

In the group with positive findings the interval between admission and roentgen examination ranged from 1 to 10 days, avergaing 3 days. In cases with negative findings the range was 5 to 17 days, excluding one examination of the oesophagus performed on the day after admission. The average interval was 9 days.

No serious complications attributable to the roentgen examination were encountered. Some patients continued to bleed as before; one patient otherwise without evidence of haemorrhage had a positive Weber test from the faeces 3 days after examination of the stomach.

The selection of patients for roentgen

examination appears to be vague in the infant group, but seems to be quite rigid in other age groups, as projected against the total of 1221 various contrast examinations of the upper G.I. tract.

Discussion

The literature concerning roentgen examination of the upper gastrointestinal tract with bleeding and/or peptic ulcer in children is largely limited to case reports with an emphasis on features encountered in the cases described. The data have not been projected against other admissions or examinations. The present study indicates that such cases are relatively rare, about one bleeding patient in every thousand at a teaching hospital, with one confirmed peptic ulcer patient for two thousand other patients. However, the condition of the child can be critical and particularly so in cases with lesions that can be demonstrated on roentgen examination. These patients also tend to develop a prolonged course of their disease, whereas the transient type of bleeding seems more rarely to reveal its underlying cause on roentgen examination. The findings vary from case to case due to their small number and great care in performing the examination and evaluating the findings is required. The examination itself is not dangerous to the patient.

The number of positive findings does not reach the level reported for adults (Ritvo *et al.*, 39; Soila 41), comprising some $\frac{3}{4}$ of the examined cases. The corresponding figures are $\frac{2}{3}$ positive findings in examined bleeders and/or peptic ulcer patients, and $\frac{1}{2}$ positive findings in bleeders only. In addition, the present material

does not serve very well as a basis for discussion concerning the infants, as they have not been subjected to a roentgen examination. The transient nature of the bleeding from fragile tissues only superficially injured seems to contribute to these results, whereas deep and permanent lesions are well revealed by roentgen examination.

Concerning other known cases of bleeding (Thomsen, 44) it is worth while to mention that 32 various diaphragmatic hernias were roentgenologically diagnosed, but there was no evidence of haemorrhage in any one of them. Most cases had been operated on or otherwise treated immediately after birth and before complications occurred. Similarly, no perforations of peptic ulcers were encountered in the present material. One case of oesophageal varices due to hepatolienal fibrosis was diagnosed several years before a bleeding episode occurred.

Summary

Twenty-six paediatric patients out of 23,000 had upper gastro-intestinal bleeding and/or peptic ulcer, the frequency being about 1:1000. Eighteen patients were subjected to roentgenological examinations, the omitted 8 all being infants. Eleven peptic ulcers were demonstrated (1:2000), involving 10 boys and one girl (10:1). Of the boys 8 had duodenal ulcers, one had a gastric ulcer and one an oesophageal ulcer; the girl had a gastric ulcer. Among the 18 patients examined there were 14 with bleeding; 7 ulcer cases were complicated by haemorrhage. Complete roentgen examinations were performed and no serious complications occurred

from the examinations. Bleeding was due to teleangiectasiae of the stomach in one case. Thus 12 out of 18 patients examined could be provided with a roentgenological diagnosis, corresponding to $\frac{2}{3}$ of the material. Eight out of the 14 bleeding patients

had a positive roentgen diagnosis, corresponding to about $\frac{1}{2}$ of the cases. Some roentgen diagnostic aspects are illustrated by case reports and the significance of the results is evaluated in the discussion.

Considérations radiologiques à propos d'hémorragies de la partie supérieure du tractus gastro-intestinal et d'ulcères gastro-duodénaux observés chez des enfants.

Sur un total de 23,000 patients pédiatriques, 26 présentaient des hémorragies de la partie supérieure du tractus gastro-intestinal et/ou des ulcères gastro-duodénaux dont la fréquence s'établit ainsi à environ 1:1000. Dix-huit de ces enfants furent soumis à des examens radiologiques; les huit autres, pour lesquels aucun examen radiologique ne fut pratiqué, étaient tous des nourrissons. Onze cas d'ulcères gastro-duodénaux furent mis en évidence (1:2000); ils se répartissaient sur 10 sujets du sexe masculin et 1 sujet du sexe féminin (10:1). Chez les garçons, on releva 8 cas d'ulcères duodénaux, 1 cas d'ulcère gastrique et 1 cas d'ulcère de l'oesophage. La fillette était atteinte d'ulcère gastrique. Sur les 18 patients examinés, 14 avaient des hémorragies; 7 cas d'ulcères se compliquaient d'hémorragies. Les malades furent soumis à des examens radiologiques complets et ceux-ci ne donnèrent lieu à aucune complication sérieuse. Dans un cas l'hémorragie était due à des téléangiectasies de l'estomac. Ainsi donc, un diagnostic radiologique a pu être posé dans 12 cas sur les 18 examinés, ce qui correspond à une proportion de $\frac{2}{3}$. Le diagnostic radiologique fut positif chez 8 des 14 malades atteints d'hémorragies, ce qui correspond à une proportion d'environ $\frac{1}{2}$. Certains aspects radiodiagnostiques sont illustrés par la description de cas cliniques suivie d'une discussion tendant à dégager la signification qu'il y a lieu d'attacher aux résultats obtenus.

Röntgenologische Betrachtungen bei Blutungen im oberen Magen-Darmabschnitt und peptischem Geschwür bei Kindern.

Sechszundzwanzig unter 23000 pädiatrischen Patienten hatten Blutungen im oberen Magen-Darmkanal und/oder ein peptisches Geschwür, ein Häufigkeitsverhältnis von ungefähr 1:1000. Ahtzehn Kranke wurden röntgenologisch untersucht, die 8 übergangenen waren Kleinkinder. Elf peptische Geschwüre wurden aufgezeigt (1:2000), die 10 Knaben und ein Mädchen betrafen (10:1). Unter den Knaben hatten 8

Zwölffingerdarmgeschwüre, einer ein Magengeschwür und einer ein Speiseröhrgeschwür. Das Mädchen hatte ein Magengeschwür. Unter den 18 untersuchten Kranken hatten 14 Blutungen; 7 Geschwürfälle waren von Blutung kompliziert. Vollständige Röntgenuntersuchungen wurden durchgeführt, ohne dass erhebliche Komplikationen durch sie verursacht waren. Blutung war bei einem Fall auf Teleangiektasien im Magen zurückzuführen. Es konnten somit 12 unter 18 Patienten mit einer röntgenologischen Diagnose versehen werden, was $\frac{2}{3}$ der Krankenserie entspricht. Acht unter den 14 blutenden Kranken, d.i. ungefähr die Hälfte der Fälle, hatten positive röntgenologische Diagnose. Gewisse röntgendiagnostische Aspekte werden an Hand der Krankengeschichten illustriert und die Bedeutung der Ergebnisse in der Diskussion ausgewertet.

Consideraciones roentgenológicas sobre las hemorragias gastrointestinales altas y la úlcera péptica en los niños.

Veintiseis pacientes pediátricos de 23000 presentaban hemorragias gastrointestinales altas y/o úlcera péptica. La frecuencia era de 1:1000 aproximadamente. Dieciocho pacientes fueron sometidos a exploraciones radiográficas, los ocho restantes eran todos ellos infantes. Se demostró la presencia de 11 úlceras pépticas (1:2000) que afectaban a 10 niños y una niña (10:1). De los niños, 8 aquejaban úlceras duodenales, uno úlcera gástrica y otro úlcera esofágica. La niña tenía una úlcera gástrica. Entre los 18 pacientes examinados 14 presentaban hemorragias; 7 casos de úlcera se hallaban complicados por hemorragias. Se practicaron exámenes roentgenológicos completos, sin que sobreviniera ninguna complicación seria. Las hemorragias eran debidas a teleangiectasias del estómago en un caso. En 12 de los 18 pacientes examinados pudo establecerse el diagnóstico roentgenológico, es decir, en $\frac{2}{3}$ de la casuística. Ocho de los 14 pacientes con hemorragias presentaron un diagnóstico radiológico positivo, es decir, aproximadamente $\frac{1}{2}$ de los casos. Se ilustran algunos aspectos del diagnóstico roentgenológico mediante la presentación de casos. En la discusión se valora la significación de los resultados obtenidos.

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Roentgenol. Dept.
Paediatric Clinic
Karolinska sjukhuset
Stockholm
Sweden

From the Children's Department, University Hospital, Oslo, Norway
(Head: Professor Leif Salomonsen)

Lipodystrophy and Gigantism with Associated Endocrine Manifestations

A New Diencephalic Syndrome?

by MARTIN SEIP

In 1954, Berardinelli (2) described from Brazil two small children suffering from what he called an until then "undiagnosed endocrino-metabolic syndrome", with the main features "acromegaloid gigantism, hepatosplenomegaly, fatty infiltration of the liver, hyperlipemia, hyperproteinemia, and disturbed carbohydrate metabolism". He found that they did not fit into any known disease entity. Although he could make no definite statements about the primary lesion causing this clinical picture, he suggested that "possibly there is some relationship to pituitary hyperfunction", and discussed the possible role of growth hormone (STH).

In the Children's Department, University Hospital, Oslo, we have studied two siblings with the same syndrome, and a third patient presenting most of the same symptoms. It has been possible to clarify several features of this strange disease and its pathogenesis. We have been able to show that it probably may be due to a hypothalamic lesion. Our three patients, therefore, will be presented in some detail, and some of the most important theoretical problems arising in this connection will be

discussed. A similar, though not identical case has been reported by Fontan *et al.* (8).

Methods

17-ketosteroids (17-KS) were determined by Vestergaard's method (21), and 17-ketogenic steroids (17-KGS) by the Diczfalussy modification (4) of Norymberski's method. ACTH-tests were performed as follows. The urine was collected in three subsequent 24-hour-periods, and the 17-KS and 17-KGS output determined for each of these periods. In the first 48 hours of the test the adrenals were unstimulated. At the beginning of the third 24-hour-period an intramuscular injection of depot ACTH (20 I.U. of the potent Norwegian preparation Jaton prolongatum, extracted from whale hypophyses) was given.

Epinephrine and norepinephrine were measured by the method of van Euler & Floding (7). Follicle-stimulating hormone (FSH) was determined as described by Klinefelter & al. (13), estrogens by the Allen-Doisy method, and pregnanediol by the procedure described by Talbot *et al.* (20).

Case Reports

Our first patient A.E. is a girl born Febr. 7, 1952, No. 3 of six siblings, two of whom are dead.

The first child in this family, a boy born 1949, died when he was less than 5 months

old. From his first week of life he had increasing jaundice, hepatosplenomegaly, and, for some days before he died, a bleeding tendency with petechiae, ecchymoses and bloody stools. He died in another hospital without any specific diagnosis being made. Autopsy was not performed.

The second child, a girl born 1950, died when three weeks old with a similar clinical

picture. From a week after birth she got progressively jaundiced. Shortly before death signs of cerebral hemorrhage developed, with a bulging fontanel, bloody spinal fluid, and marked anemia. Autopsy was not performed.

A.E. (Case 3, Table 1) was born as the first of twins following a normal gestation, 7 weeks before term. The delivery was uneventful. She weighed 2050 g. and measured 47 cm, and had definite signs of her disease. Her healthy twin brother weighed 2410 g and measured 48 cm. In 1954, another healthy brother was born, and in 1957 our second patient.

In 1952-53 A.E. was studied in the Children's Department, University Hospital, Bergen, and from Jan. 1958 to May 1958 in our Hospital (Fig. 1). Since birth she has remained emaciated in spite of a good appetite. From early infancy she showed an increased rate of growth and a gener-



Fig. 1 A.



Fig. 1 B.

Fig. 1 A. & B. A.E. Six years old.

TABLE 1. *Main clinical features of the syndrome.*

Case number and sex:	Berardinelli's cases		Author's cases ¹		
	1 ♂	2 ♂	3 ♀	4 ♂	5 ♂
Onset					
Growth rate					
Bone age					
Large hands & feet	+	+	+	+	+
Muscular hypertrophy	+	+	+	+	+
Increased muscular glycogen	?	?	+	+	+
Emaciation	+	+	+	+	+
Hyperlipemia	+	+	+	+	+
Hepatosplenomegaly (fatty infiltration)	+	+	+	+	+
Corneal opacities	?	?	+	+	+
Moderately hypertrophic external genitals	+	+	+	+	+
Brownish pigmentation	+	?	+	+	+
Hypertrichosis	+	+	+	+	+
Phlebotomegaly	+	+	+	+	+
Intelligence	Normal	Normal	Normal	Normal	Subnormal
Familial occurrence	Possible	Possible	+	+	No
Consanguinity	No	+	+	+	No
Pneumoencephalography	Not performed	Not performed	Dilated third ventricle & basal cisterns	Dilated third ventricle & basal cisterns	Dilated third ventricle & basal cisterns Brain atrophy

¹ In addition three possible cases. They died in infancy with increasing jaundice, bleeding tendency, hepatosplenomegaly, and belonged to Families 1 and 3.

alized muscular hypertrophy, giving her an athletic appearance. The abdomen has been protruding with hepatosplenomegaly, and gradually a brownish pigmentation of the skin has developed. Her scalp soon became covered with an abundance of thick, curly hair. The main features of her disease picture and the most important laboratory findings are summarised in Tables 1 and 3.

When she was 6 years old, her height was 136 cm and her weight 34.5 kg. The skin was dry with creases and folds, and marked hyperpigmentation. A moderate, general hypertrichosis without special growth of the pubic and axillary hair was present. The labia majora and clitoris were moderately hypertrophic. There was no breast development. The head was dolichocephalic (circumference 53.5 cm), the face long and narrow, her lips relatively large.

The liver was large and firm with a smooth

surface, and reached 3 fingers below the costal margin. A firm spleen could be felt 2 fingers below the costal margin. Blood pressure was 130/90–140/90, fluid intake and diuresis within normal limits. A neurologic examination revealed nothing abnormal, excepting mild dysarthria. Eyegrounds were normal without lipemia retinalis. In each cornea a horizontal band of small opacities were found. Dental development corresponded to about 8 years in the upper jaw, and about 10 years in the lower jaw. X-ray examination revealed a heavily-built skeleton with normal sella turcica, and bone age 12 years.

A muscular biopsy showed an increase in muscular glycogen. Otherwise, the muscle fibers were normal with fairly uniform diameters. No increase in connective tissue or fat was demonstrable. The subcutis contained scarce amounts of fat with degenera-

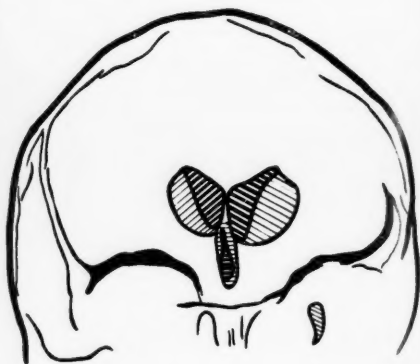
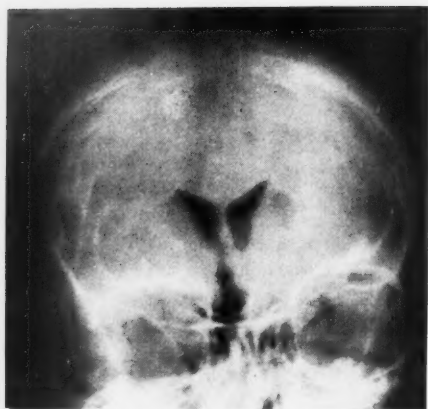


Fig. 2 A.

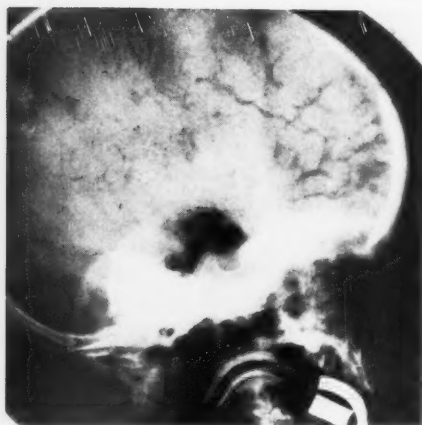


Fig. 2 B.

tive changes. The chorion showed a marked fibrous thickening. There was no increase in cutaneous or subcutaneous glycogen.

Her urine was normal. The stools contained normal amounts of fat and nitrogen. The spinal fluid was slightly cloudy, with a normal content of protein, sugar and cells. ECG, EEG and electromyogram were normal. Sex determination in blood smear showed a female pattern. A glucose tolerance curve showed the following course: 92 (F), 114 (30 min), 106 (60 min), 96 (90 min),

96 (120 min), 58 (180 min), and 86 (240 min). Blood picture and ESR were normal, and so were blood urea, serum creatinine, potassium, copper, bilirubin, CO_2 -binding capacity, total base and chlorides. The urine contained traces of copper only.

Her pneumoencephalograms are shown on Fig. 2, and her liver biopsy on Fig. 6.

Our second patient M.E. (Case 4, Table 1) is a younger brother of A.E., born Jan. 6, 1957 in breech presentation after a normal pregnancy. His birth weight was 4000 g. In



Fig. 2 C.

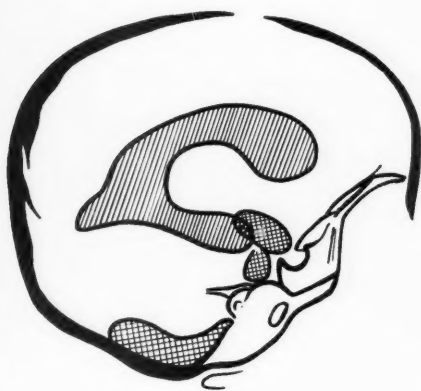
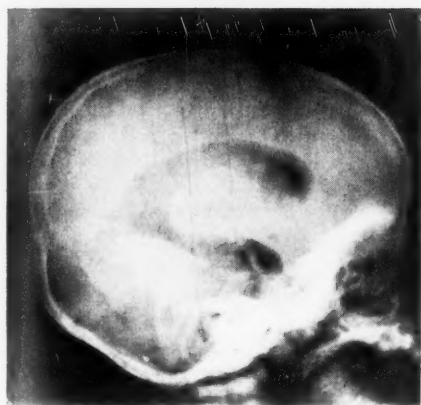


Fig. 2 D.

Fig. 2 A-D. Pneumoencephalograms of the three cases reported, A.E. (A), M.E. (B), and K.S. (C, D). Note the dilated third ventricle in A.E. and K.S., and the wide basal cisterns. In K.S. the lateral ventricles are also dilated.

his very first days of life the parents discovered that he was suffering from the same illness as his sister.

He was admitted to our Hospital when he was 1 year old (Fig. 3). His appearance closely resembled that of his sister in all main features. The hypertrichosis was, however, more pronounced. He measured 88.5 cm and weighed 12.5 kg. The abdomen was protruding, the liver reaching 3-4 fingers and the spleen 2 fingers below the

costal margin. The external genitals had the size of a several years older boy, with penile length 5 cm, and circumference 5 cm. The testes measured $2 \times 1.5 \times 1.5$ cm. Normal findings were recorded on rectal examination. A neurologic examination revealed no abnormalities. Eyegrounds were normal. The psychologist concluded that he was normally developed according to Gesell's standards. Dental development corresponded to 18 months.



Fig. 3 A. M.E. Fourteen months old.

The main laboratory data appear from Table 3. Blood picture and serum electrolytes were normal, spinal fluid, urine and stools also normal. The urine contained traces of copper only. A glucose tolerance curve showed the following course: 106 (F), 131 (30 min), 131 (60 min), 123 (90 min), 79 (120 min), 79 (180 min), 86 (240 min).

Biopsy of the skin and muscles gave exactly the same picture as in the preceding

case. The pneumoencephalograms (Fig. 2) showed dilated basal cisterns, but the ventricles were poorly filled.

Our third patient K.S. (Case 5, Table 1 is a boy, an only child born May 5, 1937. The family history is non-contributory. In the first months of her pregnancy the mother felt poorly with nausea and vomitings. She had a normal delivery two weeks before expected term. The boy weighed 2500 g. Since birth he has presented almost exactly the same picture as the two preceding cases. At three months a systolic murmur was discovered, probably due to a ventricular septal defect, and he was admitted to the ward (Fig. 4).

In infancy he was not as athletic and tall as the two other patients, but gradually he has grown more and more like them. However, this patient has shown a moderate psychomotor retardation, and a somewhat increased, though varying muscular tone, suggesting some extrapyramidal disturbance. The pneumoencephalograms show a more extensive brain lesion (Fig. 2). EEG and electromyogram are normal. ECG shows right ventricular hypertrophy.

Main clinical features of the syndrome

The main clinical features of Berardinelli's 2 and our 3 patients are tabulated in Table 1. It appears that Cases 1-4 showed almost precisely the same picture, while Case 5 is a little different on a few points.

In Cases 2-5 the disease obviously was *congenital*. The lack of subcutaneous fat was discovered already in the neonatal period, and the other features soon thereafter. In Case 1 the condition was diagnosed at 2½ years of age, but had then certainly been present for a long time, probably from birth.

Growth was markedly increased with an *acromegaloid pattern*. The patients had a strong, athletic body build, large hands

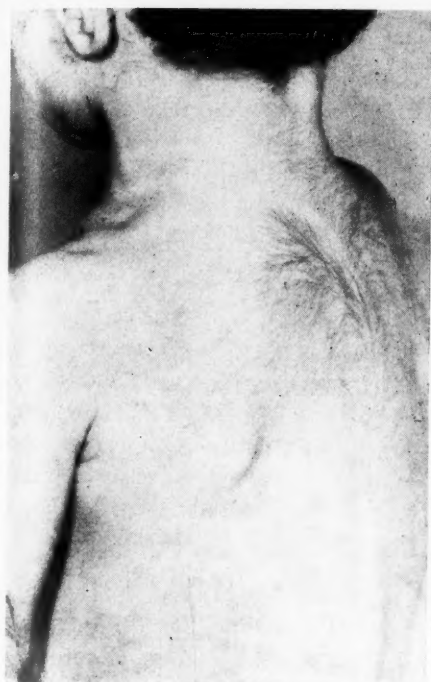


Fig. 3 B.



Fig. 3 C.

M.E. Fourteen months old.

and feet. The face showed coarse features, thick lips and projecting superciliary arches. The head circumference corresponded roughly to their height age.

Bone age was advanced in Cases 1-4, normal in Case 5.

	Age	Bone age
Case 1	6 yrs	9 yrs
Case 2	2 yrs 2 mos	6 yrs
Case 3	6 yrs	12 yrs
Case 4	13 mos	18 mos

All five patients had well developed, athletic muscles, somewhat less striking in Case 5 than in the others. Muscular biopsies showed some increase in muscular glycogen in our three cases (Fig. 5), while information on this point is lacking in

Berardinelli's paper. Otherwise normal muscle fibers without degenerative changes were observed. Fat and connective tissue were not increased.



Fig. 3 D. This figure shows the large hands with coarse skin in M.E.

Emaciation was pronounced, with extreme wasting of subcutaneous fat, even in the cheeks, and contributed to the strange, elderly look of all five patients. Histologic studies revealed a marked fibrous thickening of the chorium and de-

generative changes in the scarce amounts of subcutaneous fat present.

Hyperlipemia was a constant finding, and often made the blood serum look grayish or milky. However, the degree of hyperlipemia showed considerable fluctuations from time to time. The neutral fats were especially increased.

Hepatosplenomegaly was marked in all cases. But striking variations in the size particularly of the liver were observed within relatively short periods of time. In Case 1 the liver reached 12 cm and the spleen 15 cm below the costal margin. The liver was firm, almost hard, with small rounded knobs on the irregular surface. In Cases 2-5 the liver and spleen were palpable from 1 to 4 finger under the



Fig. 4 A.



Fig. 4 B.

Fig. 4 A. & B. K.S. Eleven months old.

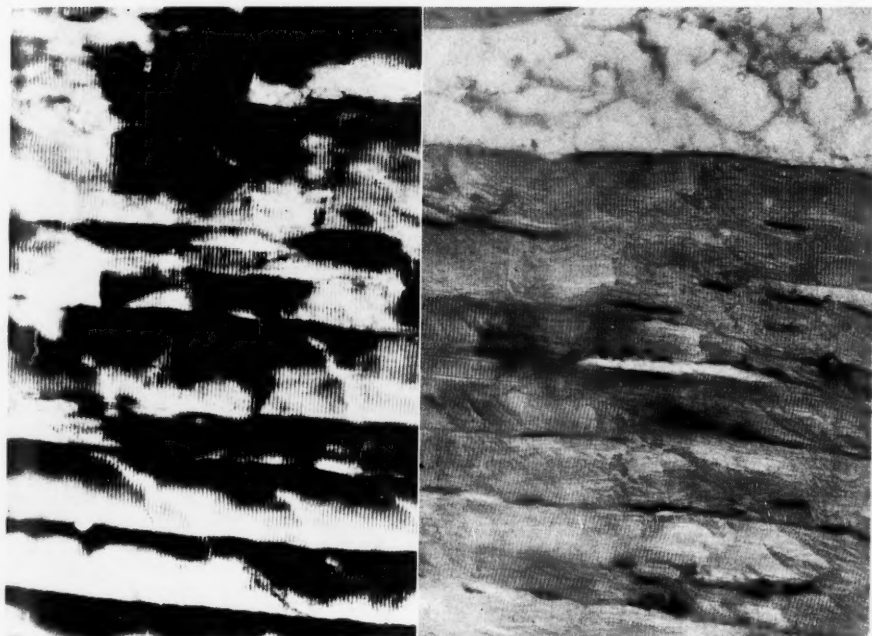


Fig. 5. *Left.* Striated muscle with increased glycogen content. PAS 200 \times .

Right. Same specimen after removal of glycogen by means of amylase from saliva. PAS 200 \times .
(Dr. E.A. Mylius, Institute for General and Experimental Pathology, University Hospital, Oslo.)

costal margin. They had a firm consistency and a smooth surface.

In Cases 1-3 *liver biopsies* were performed. In Case 1 Berardinelli found a marked "disseminated hepatic fibrosis". "In all slides examined, the hepatic parenchyma was represented by a maximum of four to five islets completely surrounded by connective tissue, in which reticulin fibers predominated." Most liver cells had one or more vacuoles, which were shown to contain neutral fats. No inflammatory cells were found. There was a high glycogen content in the liver cells outside the vacuoles. Berardinelli states, but no details are given: "Liver function tests revealed global hepatic insufficiency." This patient died at 7½ years of age from

massive gastrointestinal bleeding. Whether this hemorrhage was due to esophageal varices—which we are inclined to believe—cannot be said with certainty, as no autopsy was performed.

In Case 2 Berardinelli also found "profound alterations in the structure of the liver". There was an increase in fibrous tissue, not only between the lobules but, in certain regions, within the lobules. Most liver cells on paraffin slides were vacuolated. They had either a single and voluminous vacuole or smaller and numerous ones. The vacuole content was identified by its staining reactions as neutral fats. A few lymphocytes were found in the portal spaces, and in the interlobular fibrous tissue.

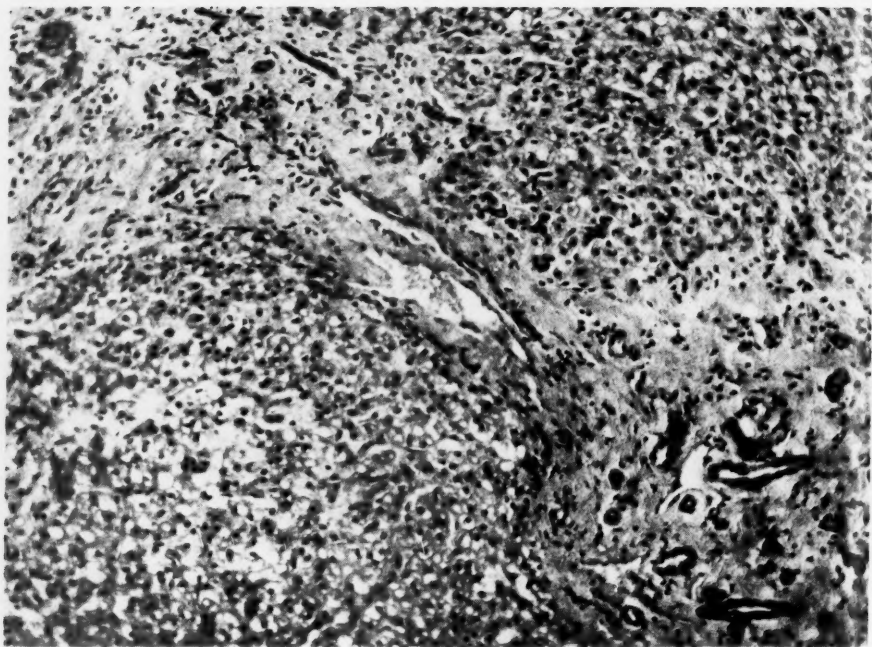


Fig. 6 A. Liver biopsy from A.E. Liver with fatty infiltration and cirrhotic changes. HES 100 \times .

In Case 3 we made essentially the same findings as described for Case 2 (Fig. 6). A marked fatty infiltration in the liver cells was the most outstanding feature. By different staining methods the fat was identified as neutral fats. No unsaturated fatty acids were found. Outside the vacuoles the liver cells were extremely rich in glycogen. There were moderate cirrhotic changes with some infiltration of lymphocytes, and a certain proliferation of small bile ducts.

Ophthalmologic examination in our three patients revealed identical pictures. Eyegrounds were normal, without lipemia retinalis. Horizontal bands of small, punctuate corneal opacities, stainable with fluorescein, were found in the superficial corneal epithelium. They resembled small,

superficial erosions, but no signs of inflammation were present. Vision did not seem to be impaired. These corneal opacities are probably due to the metabolic disturbance (hyperlipemia?). Whether these changes were present in Berardinelli's cases, is not known.

All five patients had moderately hypertrophic external genitals. The girl had a certain hypertrophy of the labia majora and clitoris, the boys of the penis, scrotum and testes. However, no obvious signs of sexual precocity were present. There was no growth of pubic or axillary hair. The girl had no breast development, menarche had not occurred. In the boys the external genitals were only moderately enlarged, and were not of the size seen in sexual precocity.

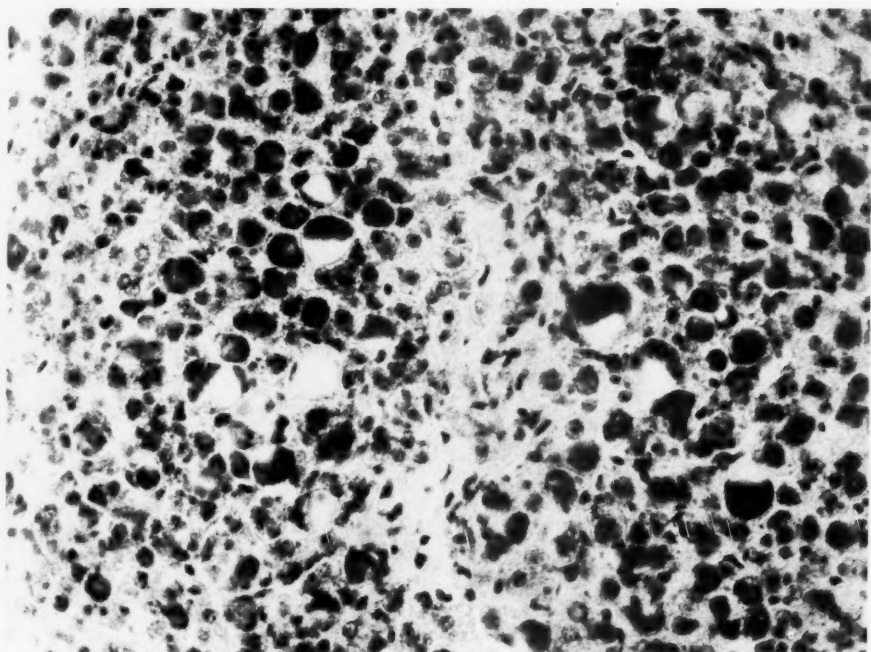


Fig. 6 B. Frozen section showing large amounts of fat in the liver cells. Sudan 200 %.

Brownish pigmentation of the skin was a prominent feature. The most intensive pigmentations were noticed in the neck, armpits, hands and forearms, but also other parts of the trunk and limbs were affected. In contrast to this, the face was remarkably pale in all five patients, even if no anemia was present. The skin was generally somewhat dry and coarse with creases and folds, resembling that of acromegals. These changes were most pronounced in the neck, hands and forearms.

A marked *hypertrichosis* was a constant finding. Fine hairs were covering most of the trunk and limbs. The scalp was covered by abundant, thick, and in our 3 cases curly hair. The hair limits were low and diffuse, whiskers being present in some of the patients.

All cases showed *thick, prominent superficial veins*, especially in the lower extremities.

In Cases 3 and 4 on radiologic examination the *heart size* seemed to be relatively large. The cardiac volume was near, but not above the upper normal limits. Information is lacking in Cases 1 and 2. It is possible that a certain increase in glycogen content might be present in the heart muscles as well as in the skeletal muscles in this condition. Case 5 probably has a congenital malformation of the heart (ventricular septal defect?).

Blood pressures were recorded in Cases 3 and 4. Slightly elevated levels were found, 130/90-140/90 and 120/80, respectively.

Pneumoencephalography was performed

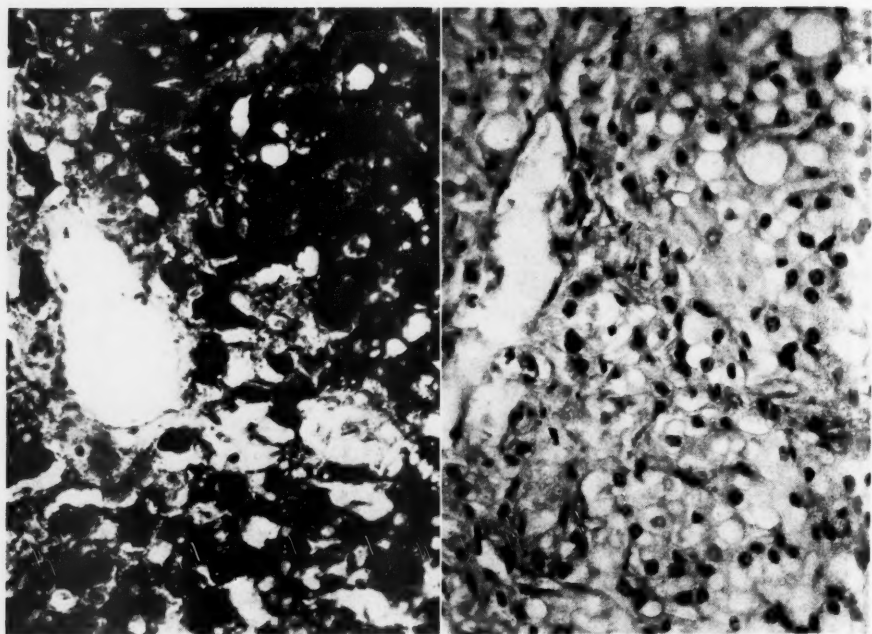


Fig. 6 C. *Left.* Liver cells with markedly increased glycogen content. PAS 200 \times . *Right.* Same specimen after removal of glycogen by means of amylase from saliva. PAS 200 \times . (Dr. E. A. Mylius, Institute for General and Experimental Pathology, University Hospital, Oslo.)

in our three patients (Fig. 2), but not in Berardinelli's. In Case 3 a moderate, though in our experience definitely pathologic dilatation of the anterior part of the third ventricle could be demonstrated. It measured up to 6 mm in breadth (normal average for her age 3 mm). The basal cisterns were dilated. Otherwise the pneumoencephalograms were normal.

In Case 4 both pneumoencephalography by the lumbar route and ventriculography were performed. The basal cisterns showed considerable dilatation. The fourth ventricle was normal, and so were the sulci on the surface of the brain. The other ventricles were not properly filled with air. While puncturing the lateral ventricles a

needle biopsy of the brain was performed. Normal brain tissue without unusual accumulation of lipids was found.

Case 5 had a more extensive brain atrophy. The third ventricle was large, measuring 13 mm. Both lateral ventricles with temporal horns and the basal cisterns showed marked dilatation. The fourth ventricle was normal. There were wide sulci on the brain's surface.

Intelligence was normal in Cases 1-4, although somewhat below average in Cases 3 and 4, whose speech development was poor. There were also some behaviour problems. The fifth patient with the more extensive brain lesion showed moderate psychomotor retardation.

TABLE 2. Serum lipids (mg/100 ml) in the apparently healthy members of the E. family.

		Neutral fats	Free fatty acids	Phospho- lipids	Choles- terol	Total lipids
Father	(1953)			367	438	
	(1958)	475	122	291	272	1160
Mother	(1953)	748	265	388	394	1795
	(1958)	366	134	358	322	1180
G.E., born 1952	(1953)	926		206	248	1380
	(1958)	390	102	249	219	960
V.E., born 1954	(1958)	441	81	294	264	1080

It is evident that the described syndrome can occur in several members of the same family. Cases 3 and 4 are brother and sister. The histopathologic studies discussed above demonstrate that an extensive fatty infiltration of the liver develops, which may produce cirrhotic changes and severe damage to the hepatic parenchyma. Particularly in Case 1 the histopathologic changes in the liver were marked, and he died from gastrointestinal hemorrhage. It is possible that the brother and sister of our patients A.E. and M.E., who died in infancy with progressive jaundice, bleeding tendency and hepatosplenomegaly, have been suffering from the same disease, with a more severe affection of the liver. This hypothesis is supported by the fact that an older sister of Berardinelli's first patient also died at 4 months of age with severe jaundice. Possibly we could include these 3 early fatal cases in our series.

Furthermore, one of the 5 siblings in Berardinelli's second family died at 11 months of age under a clinical picture of anorexia, constipation and emaciation. Case 5 is an only child, and the family history is non-contributory.

It deserves attention that in two of the families concerned consanguinity was pres-

ent. The parents of Case 2 were first cousins, and those of Cases 3 and 4 were second cousins. This could suggest a recessive inheritance of the syndrome, although the number of cases is too small for a definite conclusion to be made.

The parents of our patients A.E. and M.E., and their two apparently healthy brothers were also studied. Clinically there were no signs of the disease. However, they all had elevated serum lipids, especially neutral fats (Table 2). Phospholipids and cholesterol in some of the blood samples were moderately increased. All these blood samples were taken in the morning before breakfast.

We may conclude that the demonstrated disturbance in lipid metabolism is hereditary. The explanation seems likely, that the clinically healthy parents and brothers with only moderate alterations in fat metabolism may represent the heterozygous, and the two siblings with the fully developed clinical picture the homozygous state of a hereditary disorder.

Most important laboratory data

The most important laboratory findings appear from Table 3.

The most striking deviations from nor-

TABLE 3. *Most important laboratory data.*

Case number	Berardinelli's cases		Author's cases		
	1 ♂ 6 yrs	2 ♂ 2 yrs	3 ♀ 6 yrs	4 ♂ 13 mos	5 ♂ 10 mos
Total lipids	1200	1900	1010-5410	1050-1290	810-930
Neutral fats	—	—	445-4510	667	435
Free fatty acids	—	—	131-469	129	81
Phospholipids	—	—	82-594	78	82
Cholesterol	166	144	151-282	228-416	187-272
Foam cells, bone marrow	No	—	Yes	No	No
Total protein	8.2	10.2	7.9-9.2	7.7	6.1
Albumin	4.0	7.4	4.5-4.6	4.3	3.5
Globulin	4.2	2.8	3.3-4.7	3.4	2.6
Fibrinogen	—	—	0.5	0.5	0.15
Calcium	10.5	9-11.5	1952: 11.0 1958: 9.4	9.8	9.9-10.1
Phosphorus	3.0	5.8	1952: 6.5 1958: 4.3	4.5	4.6-7.2
Phosphatase (Bodansky U.)	3.2	7.0	1952: 16.6	9.2	11-16
Fasting blood sugar	160	121	73-94	70-106	77-97
Glucose tolerance curve	Diabetic	Flat	Flat	Flat	Flat-Normal
Creatinine excretion	—	900	854	288	80
Creatine excretion	—	—	171	162	40
17-KS	2.8	2.3	1952: 0.1-0.6 1958: 1.3-2.1	0.3-0.5	0.1-0.3
17-KGS	—	—	10.4-10.6	3.1-6.3	1.8
Circulating eosinophils	—	—	25-89	100-131	250
FSH	—	6.6 M.U.	< 6 M.U.	< 6 M.U.	—
Estrogens	—	—	1952: < 17 M.U. 1958: < 18 M.U.	< 18 M.U.	—
Pregnanediol	—	—	0.3 mg/l	0.4 mg/l	—
Epinephrine	—	—	12	0	—
Norepinephrine	—	—	4	7	—
PBI	—	—	7.6	4.3	4.9
Thyroid iodine uptake	—	—	31 %	23 %	—

mal were demonstrable in the *serum lipids*. In Case 3 the serum lipids were studied in greatest detail. In 1952-53 numerous analyses of the different fractions were performed. Within a period of some months the total lipids showed great fluctuations, from 1340 to 5410. Especially the neutral fats could be markedly elevated. Values ranging from 445 to 4510 mg/100 ml were encountered, frequently higher than 1000. The content of free fatty acids, phospholipids, and cholesterol could be normal or moderately increased. In Case 4 the serum lipids showed funda-

mentally the same pattern. Case 5 had similar, but less striking changes. Foam cells were searched for in bone marrow smears from Cases 1, 3, 4, and 5. Some were found in Case 3, but none in the others.

Serum proteins were on several occasions elevated in Cases 1-4, up to 10.2 g/100 ml. In Case 2 a relative increase in albumin, and in Cases 1, 3, and 4 a relative increase in globulin was found. The fibrinogen content of the blood was determined in our 3 patients. Cases 3 and 4 had mildly elevated levels (0.5 g/100 ml).

Serum calcium has been normal, phosphorus normal or somewhat increased, up to 7.2 mg/100 ml, phosphatase normal.

Carbohydrate metabolism was disturbed. Fasting blood sugar (Hagedorn-Jensen's method) was essentially normal. In 2 of our patients glucose tolerance curves were flat, in the third one flat and one normal curve was obtained. In these tests 1.75 g of glucose per kg body weight was given. Berardinelli's first patient showed a high fasting blood sugar and a diabetic glucose tolerance test, his second patient a normal fasting blood sugar and a flat glucose tolerance curve.

Urinary 17-KGS were repeatedly found elevated, at least in Cases 3 and 4. Urinary 17-KS were normal or slightly increased. An ACTH-test (intramuscular) failed to produce any changes in 17-KS and 17-KGS output. Determinations of epinephrine, norepinephrine, pregnanediol, FSH, and estrogens in the urine gave essentially normal results. Serum protein-bound iodine and thyroid radioiodine uptake were within normal limits, excepting a questionable, mild elevation of PBI in Case 3.

Considering the cirrhotic changes demonstrated in the hepatic parenchyma, the results of liver function studies should be of great interest. It has already been mentioned that Case 1 had signs of "global hepatic insufficiency". In our cases the results of liver function tests are not easy to evaluate. They gave no positive evidence for reduced liver function. The changes in serum proteins may be due to other causes than hepatic insufficiency. The thymol turbidity test, occasionally abnormal, is not reliable in hyperlipemic states. Owren's PP-method (measuring the combined actions of prothrombin and pro-

convertin) is a good liver function test. The results with this method were normal in all 3 cases, and so were the bilirubin and alkaline phosphatase levels.

Comments

When trying to give a unifying interpretation of this strange disease picture, the possibility of a primary hypothalamic-hypophyseal disturbance in the author's opinion deserves special consideration. Most of the clinical and laboratory findings presented may be due to *hyperfunction of the anterior pituitary gland*. Many of them may be caused by *hypersomatotropinism*: The acromegaloid gigantism, the muscular hypertrophy with increased glycogen content of the muscles, the slight cardiomegaly and hypertension, the dry, coarse skin with creases and folds, the hyperproteinemia, the hyperfibrinogenemia, the occasional hyperphosphatemia, the disturbances in carbohydrate metabolism. The effects of STH on carbohydrate metabolism are complex. The hormone in some instances can increase glucose tolerance by stimulating the pancreas to an enhanced production of insulin, in other instances through a stronger and more prolonged action, however, STH may decrease glucose tolerance (exhaustion and degeneration of the islets of Langerhans?). Thus both the flat glucose tolerance curves in Cases 2-5, and the diabetic curve in Case 1 can possibly be accounted for.

The alterations in *fat metabolism* may in part be due to hypersomatotropinism. STH mobilizes fat from the depots, increases liver fat and fat combustion. However, we have good reasons to suppose the formation of a specific, adipokinetic hormone, distinct from STH, in the an-

terior pituitary, *adipokinin* (15, 16, 17, 23). Some researchers still deny the existence of adipokinin (6), and maintain that the adipokinetic effect of pituitary extracts, first demonstrated by Best & Campbell (3), is essentially due to STH.

The observations reported in this paper are most easily explained by supposing a distinct adipokinetic hormone. The high degree of fat mobilization, hyperlipemia and fatty infiltration of the liver observed is usually not seen in acromegaly and gigantism, even though the hypersomatotropinism may be more pronounced than in our patients. The fact, that STH also possesses an adipokinetic effect does not disprove the existence of adipokinin. On the contrary, it has been shown (6) that different anterior pituitary hormones may have many effects in common (but in different degree), probably because part of the molecule may be identical or at least very similar in several hormones.

The hyperpigmentations may—if our interpretation is correct—be explained by an increase in formation of MSH.

The advanced bone age and dental development in cases 1–4 cannot be accounted for by hypersomatotropinism alone. Other pituitary hormones (TSH, ACTH, the gonadotropic hormones) are known to promote skeletal development. We have no definite evidence of increased production of gonadotropic hormones or TSH in our cases. But we have some reasons to conclude that the advanced bone age may be related to hypercorticotropinism. There are also other signs of adrenocortical hyperfunction, a high output of 17-KGS, a relatively high 17-KS output in the three oldest patients, hypertrichosis, moderate hypertrophy of the external gen-

itals, and an increase in liver glycogen. That several features of hypercorticism, e.g. the characteristic fat distribution, are lacking may be due to the complex endocrine disturbance with increased formation of adipokinin and STH.

Whether the patients will attain a remarkably great ultimate height remains to be seen. Possibly the promotion of skeletal maturation will lead to epiphysal fusion before an exceptional height is reached.

In Cases 3 and 4 intramuscular ACTH-tests were performed. But the steroid output after ACTH-stimulation remained unchanged. The explanation of this finding is obscure. Perhaps it may be that their own ACTH-production is so high, that the test dose given could produce no significant elevation in serum ACTH concentration. The circulating eosinophils were relatively low in these two patients (Table 3), and a further decrease followed ACTH administration.

In conclusion we may say that the disease picture may be explained by supposing an increased production of four anterior pituitary hormones, STH, ACTH, MSH, and adipokinin. It is reasonable to assume that a causative relationship exists between the diencephalic lesions demonstrated by pneumoencephalography, a failing hypothalamic control of hypophyseal function, and anterior pituitary hyperactivity.

There may be some doubt, whether to classify Case 5 under the same syndrome as Cases 1–4. The numerous similarities presumably are due to the possibility that the same hypothalamic structures have been damaged. But in Case 5 the brain lesion is much more extensive, and its

cause presumably quite different. It would be most correct to include Cases 1-4 in one disease entity, with Case 5 as a related, though not identical clinical picture.

Berardinelli's and our patients present a picture differing in several respects from previously reported cases of pituitary gigantism. These most often have become apparent in later childhood, although gigantism starting in infancy has been observed (1). The severe abnormalities in fat metabolism are not found. Skeletal maturation is not accelerated, and may even be retarded. Usually there is no gross evidence of hyperadrenocorticism in pituitary giants. The primary pathology probably is in the hypophysis, not in the hypothalamus. Frequently an enlarged sella turcica is demonstrable. It seems justified to class the cases reported in this paper under a separate syndrome or—this at least applies to Cases 3 and 4—even a separate, hereditary disease, which may perhaps be named congenital hyperpituitarism of hypothalamic origin.

There are obvious points of resemblance between our syndrome and the "*diencephalic syndrome of emaciation*", described by Russell (18, 22) and Dods (5), which is caused by an infiltrative astrocytoma in the anterior hypothalamus. Russell's cases also showed the same lipodystrophy despite a good appetite, and in the early stages frequently an enhanced growth rate. In the later stages the symptomatology is influenced in many ways by the growing brain tumor.

In its familial and hereditary occurrence the described syndrome is analogous to other heredofamilial diseases with affection of the hypothalamus. One such condition is the Laurence-Moon-Biedl syn-

drome, which shows recessive inheritance. Diabetes insipidus may also occur in an inherited form, mostly with dominant, sometimes with sexlinked transmission. The few autopsies performed in such cases have shown a defective development of certain hypothalamic nuclei (9). Other familial and hereditary diseases with possible or probable affection of the diencephalon are Albright's syndrome and familial dysautonomia. In lipodystrophia progressiva, which frequently is a familial disorder, lesions in the diencephalon have also been demonstrated (19).

Case 5 with the more diffuse cerebral atrophy has several points of resemblance to the congenital muscular hypertrophy described by Cornelia de Lange (10, 14) and characterized by the triad congenital muscular hypertrophy, extrapyramidal motor disturbances and mental deficiency. In de Lange's syndrome waste of subcutaneous fat and abnormal lipid metabolism are common features.

The changes in serum lipids and the deposition of neutral fats in liver and spleen are essentially the same in our patients as in idiopathic familial hyperlipemia (11, 12). Harsl f described diencephalic endocrine manifestations (infantilism, nanism) in so-called "*idiopathic familial hyperlipemia*". He thought that the endocrine symptoms were secondary to hyperlipemia with resulting lipid deposits in the hypothalamus. However, the explanation might as well be that a primary hypothalamic lesion had resulted in secondary hyperlipemia. Perhaps some cases of so-called idiopathic familial hyperlipemia are in fact due to a diencephalic disease with increased adipokinin production. In this connection the observations in the clinically

healthy parents and brothers of Cases 3 and 4 of a definite hyperlipemia with particular increase in neutral fats and to a lesser degree other lipid fractions are important.

Therapeutically Berardinelli in Case 2 tried X-ray irradiation of the hypophysis, possibly with a certain effect. We have as yet, however, hesitated to give this form of therapy to our young patients.

Summary

Three patients, two of whom are brother and sister, are presented in detail. From early infancy they showed the following main features: Acromegaloid gigantism, extreme waste of subcutaneous fat, hyperlipemia, hepatosplenomegaly with fatty infiltration of the liver and spleen, cirrhotic liver changes, abnormal carbohydrate metabolism, general muscular hypertrophy with increased muscular glycogen, hypertrichosis, hyperpigmentation, punctuate corneal opacities, advanced bone age, and perhaps slight cardiomegaly (glycogen deposits?) and hypertension. The results of the most important laboratory studies in these patients are presented.

The clinical and laboratory data in the author's opinion are most easily explained by supposing an increased formation of several anterior pituitary hormones, STH, ACTH, MSH, the adipokinetic hormone (adipokinin). Pneumoencephalographic studies revealed dilatation of the third ventricle in two of the reported cases and of the basal cisterns in all three, pointing to a hypothalamic lesion. The hyperpituitarism is thought to be due to this hypothalamic lesion. In the two cases belonging to the same family a hereditary malformation of the diencephalon is thought to be present (possibly recessive

inheritance). In this family the parents were second cousins. Both parents and two apparently healthy brothers showed definite hyperlipemia with a similar pattern as our patients, but to a lesser degree, and other signs of the disease were lacking.

Two similar cases have been reported from Brazil by Berardinelli in 1954. However, he did not give his attention to the diencephalon as the primary site of the disease.

In two of the families concerned other siblings (3 in all) have died in infancy with progressive jaundice, hemorrhagic diathesis, hepatosplenomegaly. Possibly these have also had the same disorder with a more severe affection of the liver.

The relationship of the described syndrome to several other known disease entities is discussed.

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Addendum

After the manuscript was concluded the plasma insulin activity was determined in one of the patients (K.S.) with the rat diaphragm method (Professor Otto Walaas, Oslo). A ten-fold increase in plasma insulin activity was found.

Lipodystrophie et gigantisme avec manifestations endocriniennes associées. Un nouveau syndrome diencéphalique?

Trois patients dont deux sont frères et sœurs sont présentés en détail. Depuis leur petite enfance, ils présentent les caractéristiques suivantes : gigantisme acromégaloïde, très grande déperdition de graisse sous-cutanée, hyperlipidémie, hypertrophie du foie et la rate avec infiltrations graisseuse dans le foie et la rate, changements cirrhotiques du foie, métabolisme anormal d'hydrate de carbone, hypertrophie musculaire générale avec augmentation de glycogène musculaire, hypertrichose, pigmentation excessive, points opaques sur la cornée, vieillissement des os et peut-être une légère cardiomégalie (dépôts de glycogène?) et hypertension. Exposé des résultats des plus importantes études en laboratoire sur ces patients. Les données cliniques et de laboratoire peuvent d'après l'opinion de l'auteur être aisément expliquées par la possibilité d'un accroissement dans la formation de plusieurs hormones pituitaires antérieures, STH, ACTH, MSH, l'hormone adipokinétique (adipokinine). Les études pneumoencéphalographiques ont révélé une dilatation du troisième ventricule dans deux des cas présentés et une dilatation des citernes basales dans les trois cas, ce qui dénonce une lésion de l'hypotalamus. On soupçonne dans les deux cas appartenant à la même famille une malformation héréditaire du diencéphale (probablement un atavisme récessif). Dans cette famille, les parents étaient cousins au second degré. Chez les deux parents et chez deux frères apparemment saine on trouve une hyperlipidémie prononcée du même type que celle de nos patients, mais à un degré moindre, et les autres signes de maladie n'existent pas. Deux cas similaires ont été signalés au Brésil par Berardinelli en 1954. Cependant il ne reconnut pas le diencéphale comme siège initial de la maladie. Le rapport entre le syndrome décrit et d'autres maladies est discuté.

Lipodystrophie und Riesenwuchs mit assoziierten endokrinen Erscheinungen. Ein neues Zwischenhirnsyndrom?

Es wird ein detaillierter Bericht über drei Patienten, zwei von ihnen Bruder und Schwester, gegeben. Seit ihrer frühesten Kindheit zeigten sie folgende hauptsächlich Symptome: akromegaloïden Riesenwuchs, extreme Atrophie des Unterhautfettgewebes, Hyperlipämie, Hepatosplenomegalie mit fettigen Infiltrationen von Leber und Milz, zirrhatische Leberveränderungen, anomalen Kohlehydratstoffwechsel, allgemeine Muskelhypertrophie mit erhöhtem Muskelglykogen, Hypertrichose, Hyperpigmentierung, punktförmige Hornhauttrübungen, vorgeschrittene Knochenentwicklung, möglicherweise leichte Kardiomegalie (Glykogendepots?) und

Hypertonie. Es werden die Ergebnisse der wichtigsten Laboratoriumsversuche an diesen Patienten vorgelegt. Die Ergebnisse lassen sich nach Ansicht des Autors am leichtesten erklären, wenn man eine vermehrte Bildung von verschiedenen Hypophysenvorderlappenhormonen annimmt: STH, ACTH, MSH und adipokinisches Hormon (Adipokinin). Pneumoencephalographische Untersuchungen ergaben eine Erweiterung des dritten Ventrikels bei zweien der erwähnten Fälle und der basalen Zisternen bei allen dreien, was auf eine Hypothalamusläsion hindeutet. Bei den zwei zur selben Familie gehörenden Fällen wird das Vorhandensein einer erblichen Mißbildung des Zwischenhirns angenommen (möglicherweise rezessive Vererbung). In dieser Familie waren die Eltern Vettern zweiten Grades. Beide Elternteile und zwei anscheinend gesunde Brüder zeigten eine definierte Hyperlipämie mit einem ähnlichen Bild wie das unserer Patienten, jedoch in geringerem Grade; andere Symptome der Krankheit fehlten. Zwei ähnliche Fälle sind 1954 von Berardinelli aus Brasilien berichtet worden. Er richtete sein Augenmerk jedoch nicht auf das Zwischenhirn als primärem Krankheitsherd. Es werden die Beziehungen des beschriebenen Syndroms zu verschiedenen anderen bekannten Krankheitseinheiten diskutiert.

Lipodistrofia y gigantismo con manifestaciones endocrinas asociadas. ¿Un nuevo síndrome diencefálico?

Se presentan con detalles tres pacientes, dos de ellos hermano y hermana. Desde su primera infancia, mostraron los siguientes fenómenos principales: gigantismo acromegaloïde, atrofia extrema de la grasa subcutánea, hiperlipemia, hepatosplenomegalia con infiltración grasosa del hígado y bazo, degeneración cirrótica del hígado, metabolismo hidrocarbonado anormal, hipertrofia muscular general con glicógeno muscular incrementado, hipertrichosis, hiperpigmentación, opacidades corneales puntiformes, avanzado desarrollo óseo, probablemente ligera cardiomegalia (¿depósitos de glicógeno?) e hipertensión. Se presentan los resultados de los estudios de laboratorio más importantes realizados sobre estos pacientes. Los datos clínicos y de laboratorio se explican, según opinión del autor, mejor suponiendo una hiperproducción de diversas hormonas de la adenohipófisis, STH (hormona somatotropa), ACTH (hormona adrenocorticotropa), MSH (hormona melaninostimulante) y la hormona adipocinética (adipocinina). Los estudios pneumoencefalográficos revelaron una dilatación del tercer ventrículo en dos de los casos referidos y de las cisternas basales en los tres, lo cual indica una lesión hipotalámica a la que se cree que se debe el hiperpituitarismo. En los dos casos pertenecientes a la misma familia, se cree que existe una malformación hereditaria del dience-

falo (posiblemente herencia recesiva). En esta familia, los padres eran primos segundos. Ambos y además dos hermanos, aparentemente sanos, mostraron una hiperlipemia definida con un cuadro similar al de los pacientes en cuestión, pero en grado inferior, careciendo de otros fenó-

menos de la enfermedad. Berardinelli informó, en 1954, sobre dos casos similares del Brasil sin fijarse, no obstante, en el diencefalo como localización primaria de la enfermedad. Se discuten las relaciones que tiene el síndrome descrito con varias otras entidades patológicas conocidas.

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Children's Department
Rikshospitalet
Oslo
Norway

Fig

From the Department of Paediatrics, Rigshospitalet, Copenhagen, Denmark.
(Chief: Professor Preben Plum, M.D.)

A Method to Register the Head Circumference in Infants

by ERIK TERSLEV

In the attempt to establish an exact and at the same time clear and easily accomplished way to register the growth of the head circumference of the newborn, where suspicion of pathologic dimensions has been aroused, the Department of Paediatrics, Rigshospitalet, Copenhagen, has introduced the use of graphpaper¹ subdivided

¹ Manufactured by the firm A. G. Frisenette, Lyngby, Denmark.

into months and days from January the 1st to December the 31st, on which the normal curves are drawn up. The recording of the curve for the mean circumference together with the two curves, within the limits of which 80 % of the measures occur (10 % falling above, 10 % below) is done by use of a templet (Fig. 1). This templet is made of transparent acrylplasticplate, on which the original curves (Silver &

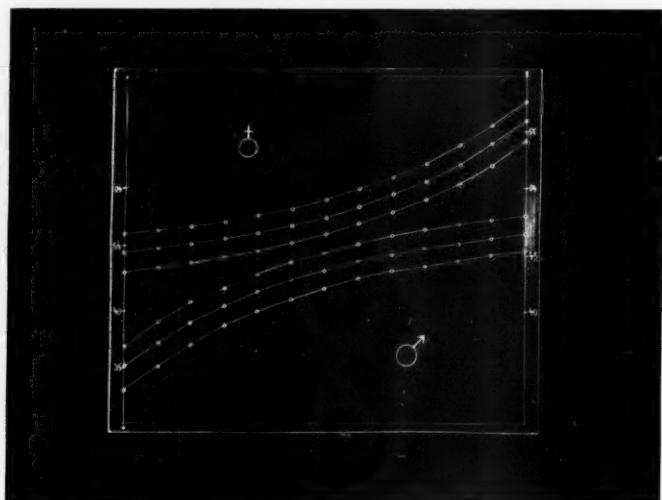


Fig. 1. Templet of acrylplasticplate with standard curves for head circumference of boys and—turned 180 degrees—girls, from 0 to 12 months.

Deamer) are engraved. The curves are transferred to the graphpaper for instance by marking with a sharp pencil through the holes of the plate, situated according to the curves with the interval of one month. Starting at the marks the curves can now be fully drawn up. Zero is placed at the birthdate, thus simplifying the daily task of recording the measurements on the graphpaper as the found value can

be entered accurately on the date of measuring. The inconvenience of having to calculate with fractions of months is hereby avoided.

Such curves transferred to the special graphpaper by means of a templet can advantageously also be used in other controlmeasureings, where the normal values deviate greatly in proportion to the age.

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Department of Paediatrics
Rigshospitalet
Copenhagen
Denmark

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Renal Function Studies in Infants and Children with Acute, Nonobstructive Urinary Tract Infections

by JAN WINBERG

In an earlier communication (24) the results of an investigation into the renal concentration and dilution capacity in six cases of acute urinary tract infection were reported. At the same time earlier observations stimulating such an investigation were presented. The findings suggested a similar type of renal damage in these acute cases as in those with chronic infections. The demonstration that a clinically mild urinary tract infection could be associated with marked impairment of renal function was the reason for further research into the nature and extent of renal damage in these cases.

In the present paper an account will be given of investigations of true endogenous creatinine clearance, acidification, and concentration capacity in 22 infants and children with a recent acute urinary tract infection. Since it has been shown that in cases with obstructive malformations and urinary tract infections serious renal damage may appear very early (i.e. 1, 25), only patients in whom a thorough urological investigation has excluded the presence of obstruction are included in this material.

Material and Methods

The material consisted of 22 patients, who had had an acute urinary tract infection and in whom a thorough urological investigation had failed to reveal any obstructive malformations of the urinary tract. The criteria for the diagnosis were described in a previous paper (24). The sediment was considered to be positive with 5 leucocytes or more per high power microscopic field. The composition of the material with regard to age, sex, number of previous infections and duration of fever is given in Table 1. The clinical symptoms were mild in all cases. All became afebrile within 1-3 days after institution of adequate therapy.

Intravenous urography was performed in all cases. Micturition urethrocystography was carried out as described by Kjellberg, Ericson & Rudhe (11), and was performed in all but one. The results are summarized in Table 2. Duplication of the upper urinary tract was seen in four out of twelve cases above one year of age, but in none below this age. No obvious hypoplasia of the kidneys could be demonstrated on the roentgenograms.

The renal concentration capacity of Cases 1, 5, 6, 7, 10 and 12 was reported in a preliminary communication (24).

True endogenous creatinine clearance was in most instances determined during 24-hour periods, as described earlier (26). A clearance

TABLE 1. *Relevant clinical data of the patients investigated.*

Case no.	Sex	Age in years	Number of previous infections	Duration of fever in days ¹	Note
1	female	1 ¹ / ₂ /12	None	2	Heavy bilateral reflux
2	female	3/12	None	5	
3	female	3/12	One (?)	4	
4	female	4/12	None	3	
5	male	4/12	None	11	
6	male	4/12	None	5 ¹	
7	female	6/12	None	6	Slight bilateral reflux
8	female	8/12	None	5	
9	female	10/12	None	6	
10	female	11/12	None	8	
11	female	12/12	Several	1	²
12	female	15/12	None	3	
13	female	3	None	4	
14	male	5	None	16	²
15	female	5	None	4	
16	female	6	Several	A few days	Heavy bilateral reflux
17	female	7	None	6	
18	female	9	Several	5	
19	female	9	Several	3	²
20	female	10	Several	3	
21	female	11	None	Only subfebrility	²
22	female	15	One	3	

¹ By fever is meant 38° centigrade or more. The temperature fell rapidly to afebrile levels in all cases except no. 6. This patient remained subfebrile for 2-3 weeks. The data concerns the infection preceding the renal function studies.

² Duplication of the upper urinary tract.

TABLE 2. *Summary of the roentgenological findings.*

	Number of cases below 1 year of age	Number of cases above 1 year of age
<i>Intravenous urography</i>	10	12
Essentially normal findings	10	8
Unilateral duplication of the upper urinary tract	0	3
Bilateral duplication of the upper urinary tract	0	1
<i>Micturition urethro-cystography</i>	9	12
No vesico-ureteral reflux	5	8
Unilateral vesico-ureteral reflux	2	3
Bilateral vesico-ureteral reflux	2	1

value below the lower 2 σ -limit for normal cases was termed subnormal.

In some instances it was impossible to obtain a 24-hour urine collection. In these

cases short term determinations were performed in the following manner. The patients were hydrated prior to, and if possible, during the experiment. A multi-held

catheter, the tip of which was smeared with an anesthetic jelly, was inserted into the bladder. When a high diuresis was achieved the clearance periods were started. Before the beginning of the first clearance period and at the end of each period the bladder was rinsed twice with 25-50 ml of physiological saline, and finally by insufflation of air and suprapubic pressure. Three to five collections were performed in each of the 13 short term clearance determinations recorded in Fig. 3. The duration of the collection periods varied between 16 and 88 minutes. Immediately after the last period was completed a blood specimen was drawn.

The concentration capacity was determined after water deprivation for 12-16 hours combined with the administration of pitressin tannate in oil, as described in a previous paper (27). If the maximum urine solute concentration attained in a test was below the lower 2 σ -limit for normal cases, the concentration capacity was termed subnormal. Such a subnormal capacity can in most instances be assumed to be due to renal damage, but might in some instances be caused by the influence of undue factors upon the concentration mechanism.

In some few instances, specially referred to in the text, pitressin tannate was not given. The period of water deprivation was in these cases prolonged to 17-18 hours.

The ability of the patients to lower the pH of urine after an acid load was investigated. Ammonium chloride was given in a total dose of 5-6 g (90-110 mEq) per sq.m. body surface area per 24 hours. This dose was divided into four equal parts, given at 6 hourly intervals beginning at 12 noon one day. Next morning about 8 a.m. with the patient fasting, a urine specimen was collected under mineral oil, and the pH determined in a Beckman pH meter.

Results

Renal concentrating power

It is seen in Fig. 1, that of the 10 tested cases below one year of age the urine solute concentration was subnormal in

eight.¹ In the remaining two cases the solute concentration measured was low, but within normal limits. In the twelve cases above one year of age the solute concentration before therapy was subnormal in nine and within normal limits in three (Fig. 2).¹ The concentration test was found to yield urines of lower concentration during the second (and third) test than during the first one in three cases (Cases 6, 8, 10). In Case 6 this decrease occurred during a three week period of subfebrility, following the febrile stage. The figures show that, disregarding this initial fall of the solute concentration, repeated concentration tests performed after institution of adequate therapy yielded urines with a steadily increasing solute concentration. This increase was in some cases still noted during the 5th-6th week of afebrility (Table 3). The dilution capacity, being normal in the cases reported in the preliminary report, has not been especially investigated in the cases of the present study.

Renal acidification capacity

Seventeen patients were examined (Table 3). Ten of the patients were investigated during the first two weeks following subsidence of fever. In five of the seven cases, examined after the second week, the concentration capacity had not reached its peak value when the acidification capacity was determined.

Fourteen patients lowered the pH to

¹ Cases 10 and 12 were deprived of water for 17-18 hours but no pitressin tannate was given. The osmolal concentration in these cases was calculated from the specific gravity values by use of the regression lines for specific gravity and osmolality given in a previous article (27), taking the mean of the two values obtained, one from each regression line.

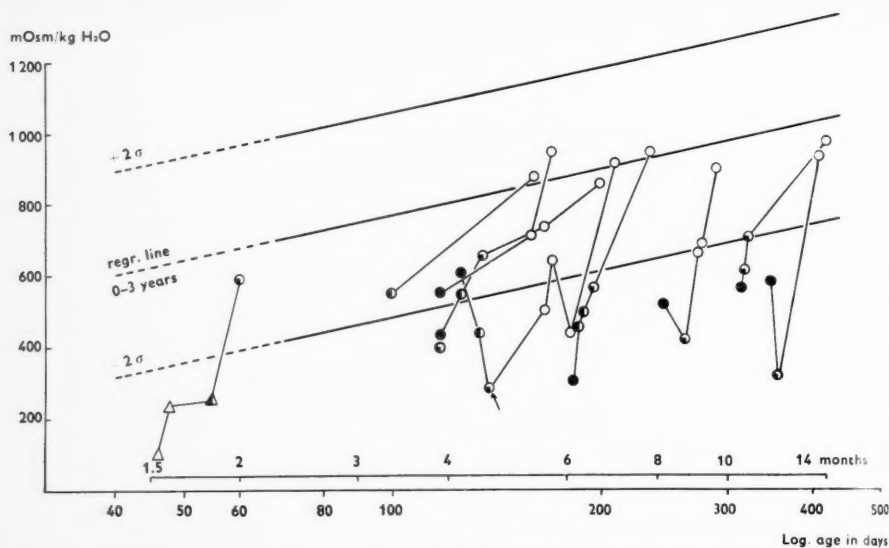


Fig. 1. Renal concentrating power in ten infants following an acute urinary tract infection as correlated to the logarithmic age of the subject. Regression line $\pm 2\sigma$ -limits for concentration capacity in infants without renal disease is also given.

In Case 6 (indicated by arrow) subsidence of fever was followed by a three week long period of subfebrility.

● concentration test 1st week after subsidence of fever. ◐ concentration test 2nd week after subsidence of fever. ◑ concentration test 3rd week after subsidence of fever. ○ concentration test > 3 weeks after subsidence of fever. Triangles: water deprivation for 6–11 hours only.

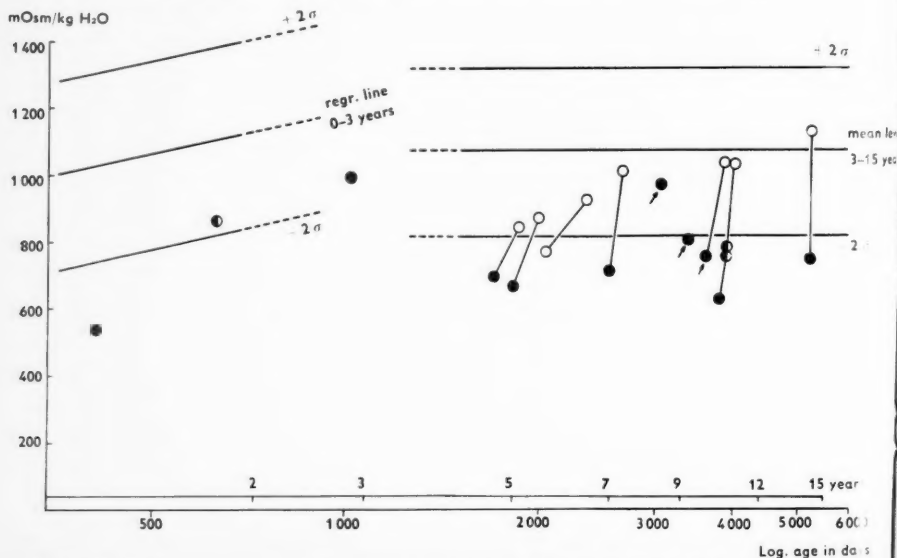


Fig. 2. Renal concentrating power in twelve children following an acute urinary tract infection as correlated to the logarithm of the age of the child. The regression line and mean level $\pm 2\sigma$ -limits for concentration capacity in children without renal disease is also given. Cases 18, 19 and 20 (see text) are indicated by arrows. Symbols as in Fig. 1.

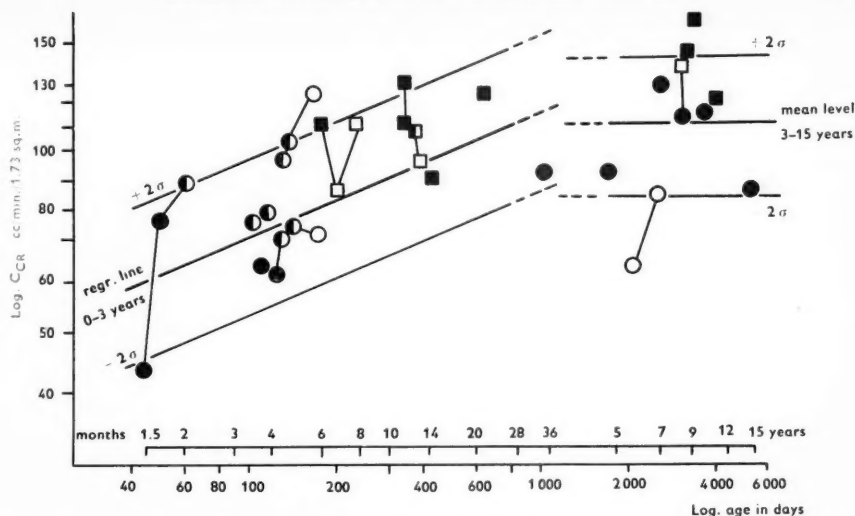


Fig. 3. True endogenous creatinine clearance in infants and children following an acute urinary tract infection correlated to the age of the subject. Regression line and mean level $\pm 2\sigma$ -limits for infants and children without renal disease are also given. Logarithmic scales. Subnormal values in Cases 1 and 16.

Circles: Every value represents a mean of the 24-hour-clearances given in Table 4. Squares: short term clearance. ●, ■ clearance 1st week after subsidence of fever, ○, □ clearance 2nd week after subsidence of fever.

TABLE 3. Renal concentrating power after third week of afebrility and pH of urine after ingestion of NH_4Cl .

Case	Renal concentrating power (mOsm/kg H_2O) after 3rd week of afebrility ¹	pH of urine after ingestion of ammonium chloride ¹	Case	Renal concentrating power (mOsm/kg H_2O) after 3rd week of afebrility ¹	pH of urine after ingestion of ammonium chloride ¹
1	—	—	9	965 (13)	4.44 (2-3)
2	872 (9)	—	10	928 (9) ²	4.62 (1-2)
3	—	4.75 (2-3)	11	—	5.13 (1-2)
4	a) 706 (6) b) 940 (8)	4.51 (0-1)	12	—	4.86 (1-2)
5	a) 732 (6) b) 849 (11)	4.70 (1-2)	13	—	5.22 (0-1)
6	a) 499 (6) b) 637 (6) c) 438 (7) d) 908 (12)	4.50 (2-3)	14	844 (16)	—
7	942 (8)	4.91 (2-3)	15	872 (25)	4.62 (1-2)
8	a) 659 (4) b) 681 (5) c) 890 (6)	4.93 (5)	16	a) 767 (5) b) 929 (52)	5.03 (5-6)
			17	1011 (16)	—
			18	—	4.53 (1-2)
			19	—	4.87 (0-1)
			20	1035 (40)	4.80 (3)
			21	1035 (4) ²	4.70 (0-1)
			22	1133 (3) ³	—

¹ Figures within brackets show number of weeks after subsidence of fever.

² Pitressin not given.

³ Pitressin not given. Specific gravity estimated. For calculation of the osmolal concentration, see footnote page 579.

TABLE 4. *The 24-hour true endogenous creatinine clearance following an acute urinary tract infection.*

Case	Clearance period	24-hour C_{CR} ml/min./1.73 sq. m.	Plasma creatinine mg/100 ml	Hematocrit	Diuresis ml/24 h.	Weighted urine loss, g
1	I	49 39	0.46	39	460 345	0 0
	II	77 79	0.33	38	750 660	0 50
	III	95 82	0.33	55	770 515	20 0
2	I	79 74	0.30 0.33	34 32	635 575	0 0
3	I	79 79 82	0.32	34	535 520 405	0 0 0
4	I	64	0.38	34	425	15
5	I	56 67 65	0.34	—	280 520 480	15 45 40
	II	72	—	—	520	35
	III	75	0.34	38	520	0
	IV	67 79	0.33	35	480 630	0 0
6	I	82 107 107	0.26	—	500 650 530	0 0 0
	II	102 108	0.23	—	530 570	0 0
6	III	113 140	0.24	34	755 690	40 15
13	I	88 98	0.49	37	670 675	45 0
14	I	99 89	0.48	36	1025 710	
16	I	64 66	0.63	39	235 195	
	II	87 79 90	0.61 0.55	40 41	295 185 495	
17	I	142 133 114	0.41	36	610 525 760	
18	I	106 124	0.39	—	550 1360	
20	I	115 122	0.47 0.51	36 31	450 1560	
22	I	82 100 85	0.70	40	1390 1800 700	

between 4.44–4.93, which was considered normal (cf. 8). In three cases the lowest pH observed was slightly above 5.0. In two of these (Cases 13 and 16) ammonium chloride was administered only for 20 hours; hence it is impossible to decide whether there was an acidification deficiency or not. In Case 11, 44 hours of ammonium chloride administration to a total dose of 12 g/sq.m. body surface area failed to lower the pH below 5.13. Since

the pH of the urine from this patient did not increase on standing neither in room temperature nor at 37°C for one and two hours respectively bacterial ammonia formation probably was not the cause of the failure to lower the pH below 5.0.

Endogenous true creatinine clearance (C_{CR})

C_{CR} was not performed in three patients (Cases 8, 9, 15).

The 24-hour clearance values recorded



Fig. 4. Case 1. Micturition urethrocytography, frontal view. Massive bilateral reflux with dilatation of ureters and pelvices was demonstrated a few days after the onset of infection when C_{CR} was subnormal. Pictures essentially unchanged 2 months later, when C_{CR} was normalized. The roentgenogram is from the latter occasion.

in Fig. 3 (circles) are in most instances means derived from two or three consecutive 24-hour clearances (see Table 4).

Subnormal values for the 24-hour C_{CR} were found in two patients (Cases 1 and 16); one investigated at the age of 6 weeks, the other at the age of 6 years. In neither were there any clinical signs of dehydration; hence there is no reason to believe that the low C_{CR} was prerenal in origin.

The clinical picture of these patients differed from that of the others in one respect: both showed a massive bilateral vesico-ureteral reflux during micturition causing a marked dilatation of the upper urinary tract (Fig. 4). The increase in C_{CR} seen in both cases after treatment took place in spite of persisting reflux.

Clearance values obtained in short term experiments can be supposed to be some-

what higher than those obtained during 24-hour collection periods (19). Since the short term C_{CR} values (the squares of Fig. 3) in all cases with the exception of Case 11, were lying above the regression line, and in four instances above the upper 2 δ -limit for normal 24-hour C_{CR} , it seems probable that in most cases also the 24-hour C_{CR} should have been within normal limits.

Case 18 was investigated in connection with two acute episodes, about 4 months apart. The first time a 24-hour clearance was performed. Next time a short term clearance study was carried out.

Discussion

The investigation was aimed at a study of the effect upon renal function of acute nonobstructive urinary tract infections with special reference to concentration and acidification capacity and true endogenous creatinine clearance. In 20 of the cases the examinations performed have been considered as elucidating this problem. In two of the cases with recurrent infections (Cases 11 and 16) it was doubtful whether there was any healing of the infections between the febrile episodes. Therefore it cannot be excluded that in these cases the changes in renal function found were due more to a chronic, progressive infection, rather than to the acute episodes.

It has been shown in an investigation of healthy children that subnormal values for the concentration capacity, obtained in individual cases, should be evaluated cautiously, since undue factors may influence the concentrating power in a limiting direction (27). If, however, the patients

in the present study are looked upon as a group, it is evident that this group is characterized by a decreased ability to produce a concentrated urine during the weeks following infection. In a majority of the cases this functional impairment persisted after normalization of the urinary sediment. A restoration of the concentration capacity after treatment is obvious. In most cases it is difficult to decide when it is completed, since a considerable physiologic variation of this function must be allowed for. A trend towards a rise of the urine solute concentrations is shown; in some cases persisting 4-6 weeks after subsidence of fever. This might indicate that the recovery is still going on at that time. This would be in accordance with the demonstration that the phenol red excretion time, which may be prolonged in pyelonephritis, sometimes is not normalized until 4-8 weeks after institution of therapy (12).

In the preliminary report on the concentration capacity in acute urinary tract infections referred to above (24), the possible causes of the decrease in the concentration capacity were discussed. Damage to the collecting ducts was considered to be the most probable cause, although coexisting damage to the distal tubules could not be excluded. The extended study presented here gives no reason to change this opinion. In the quoted article reference was also made to the similarity of the renal function pattern in acute and chronic pyelonephritis as regards dilution and concentration capacity.

The investigation of the renal acidification capacity was thought to elucidate further tubular function in those types of urinary tract infections investigated

here. The H^+ secretion is according to Pitts, Gurd, Kessler & Hierholzer (17) localized mainly to the distal tubules, but recently Ullrich & Eigler (23) have shown that it occurs also in the collecting ducts of the mammalian kidney. An analysis of the results obtained showed that there was no obvious impairment of the acidification mechanism. Whether this was due to intact distal tubules, or to the fact that the function investigated might have been relatively unaffected even in the presence of damage to the structures involved in the production of an acid urine, remains obscure.

The creatinine clearance was within normal limits in all but two cases. These findings suggest that the glomerular filtration rate was relatively normal. Limited glomerular damage or impaired drainage of a small part of the nephrons causing minor changes in the glomerular filtration rate might have escaped discovery. From a quantitative point of view this must have been much less than the change of the function of the collecting ducts.

The fact that subnormal C_{CR} was seen only in the two cases with massive bilateral vesico-ureteral reflux is worthy of some comment. It has been shown (11), that infection in some way is the determining factor in the development of vesico-ureteral reflux. Talbot (22), on the basis of comparative histological and roentgenological studies, suggested that the reflux and the dilatation were caused by inflammatory cellular infiltrations of the walls of the upper urinary tract. The most interesting finding was, however, that there seemed to be a close correlation between the histological changes of the upper part of the ureter and the

interstitial tissue of the kidney. Although definite proof for such a parallelism still seems to be lacking, the demonstration of a low C_{CR} in the two cases with heavy bilateral reflux is in agreement with the concept of Talbot, that in cases with marked dilatation of the upper urinary tract considerable inflammatory lesions of the kidney itself can be expected. Since the creatinine clearance became normalized in spite of persisting reflux it seems probable that the lowering of C_{CR} was caused by inflammatory lesions and not by the effect of the reflux on renal hemodynamics. This is however a problem deserving of more investigation.

If thus the two patients with massive bilateral reflux showed signs of serious renal damage, it is notable that three of the patients with recurrent pyelonephritis (Cases 18, 19 and 20) showed not only a normal creatinine clearance and acidification capacity but also urine solute concentrations higher than in most of the other cases, (Fig. 2). An explanation for this would be the existence in these cases of localized renal dysplasia, predisposing to relatively limited infections (4, 5, 6, 15).

Reports of renal function studies in childhood urinary tract infections are sparse. Linneweh (12) found a prolongation of the phenol red excretion time and even an elevation of the plasma non protein nitrogen level to be common. However, the incomplete information as regards occurrence of chronic infections, renal hypoplasia and obstructive malformations makes a comparison between his study and the present one difficult.

The investigations performed have shown that even the clinically mild so

called cysto-pyelitis in infants and children is a disease which as a rule also involves the renal parenchyma. Thus, this disease does not in that respect differ from acute cases running a fatal course. The findings suggest damage of the medullary situated parts of the nephron. This is in agreement with histological changes in acute fatal human pyelonephritis, characterized mainly by tubular and interstitial lesions with glomerular preservation (2, 10, 20), and investigations performed in rabbits showing the renal medulla to be much more susceptible to infection than the renal cortex (7, 9, 18).

It is a general clinical experience confirmed by several follow-up studies (13, 14, 21, 28) that recurrences of urinary tract infections are rather common even in the absence of gross obstructive malformations of the urinary tract. de Navasquez (3) and Rocha, Guze, Freedman & Beeson (18) have shown that coliform infections will easily develop in tubules obstructed and dilated by scars after healed experimental pyelonephritis or mechanical lesion of the renal papilla.

The probable damage to the most distal parts of the nephron even in clinically mild urinary tract infections suggests the possibility of scar formation causing micro-obstructive lesions of nephrons, such as described by Oliver (16) in chronic nephropathy, with resulting enhanced susceptibility to infections.

As pointed out earlier the demonstration of parenchymal involvement gives emphasis to the necessity of using chemotherapeutic doses sufficient to establish a high concentration within the renal parenchyma. The possibility that the inflammatory lesions are not healed until 4-6

weeks after subsidence of fever, might be one reason for long term treatment of urinary tract infections.

Summary

Twenty-two infants and children, thoroughly investigated from the urological point of view and found to have no obstructive malformations, form the basis for this investigation of the influence of acute urinary tract infection on renal function. The infections have in all instances been mild—of the type often classified as pyelitis.

The concentration capacity was found to be subnormal in 17 cases. The duration of this functional incapacity was difficult to establish. In some cases it possibly lasted for 4-6 weeks after subsidence of fever. The urinary findings were normalized in the majority of the cases when there was still a probable functional impairment.

The endogenous true creatinine clearance was subnormal only in two cases—the only two with massive bilateral vesico-ureteral reflux. In both these cases the C_{CR} became normalized after treatment of the infection in spite of persistence of the reflux. The significance of these findings are discussed. C_{CR} was not investigated in three cases.

The acidification capacity was investigated in 17 cases. No obvious impairment was found.

The investigation shows that there is often an involvement of the renal parenchyma in the common acute urinary tract infection. The demonstration of this fact is further support for the opinion that these infections should be treated with chemotherapeutic agents in doses suffi-

cient to give high concentrations within the renal parenchyma. The duration of the treatment is discussed in the light of the findings. Possibly the results lend support

to the opinion that these infections should be treated chemotherapeutically for several weeks after the disappearance of clinical signs and symptoms.

Étude de la fonction rénale chez des nourrissons et des enfants au cours d'infections, sans signe d'obstruction, du tractus urinaire.

Un groupe de vingt deux nourrissons et enfants, qui ont été examinés du point de vue urologique et chez qui aucune malformation entraînant une obstruction des voies urinaires n'a été trouvée, a permis d'étudier l'influence des infections du tractus urinaire sur la fonction rénale. Dans tous les cas, les infections furent bénignes et peuvent être rangées sous le terme, souvent utilisé, de « pyélocystite ».

Le pouvoir de concentration était inférieur à la normale dans 17 cas. La durée de ce trouble fonctionnel fut difficilement déterminée; dans certains cas il a persisté quatre à six semaines après la chute de la température. Dans la majorité des cas, les examens d'urine ne montraient plus rien d'anormal alors qu'il existait encore un trouble fonctionnel très probable.

La clearance de la créatinine spécifique endogène était en dessous de la normale dans deux cas seulement : seuls, ces deux enfants présentaient un reflux bilatéral vésico-urétéral très important. Dans les deux cas, la clearance de la créatinine (CC_R) est devenue normale après le traitement bien que le reflux persistât. L'interprétation de cette observation est discutée. Dans trois cas, la CC_R n'a pas été étudiée.

Le pouvoir d'acidification a été étudié dans 17 cas; aucun trouble manifeste n'a pu être démontré.

Cette étude montre qu'il existe souvent un trouble au niveau du parenchyme rénal au cours des infections banales du tractus urinaire; ceci constitue un argument pour affirmer que ces infections doivent être traitées à l'aide d'agents chimiothérapiques à des doses suffisantes pour atteindre une concentration élevée au niveau du parenchyme rénal. A la lumière de ces constatations la durée du traitement est discutée. Les résultats semblent indiquer la nécessité d'un traitement chimiothérapique qui serait poursuivi pendant plusieurs semaines après la disparition de tout signe clinique d'infection urinaire.

Nierenfunktionsstudien bei Säuglingen und Kindern mit akuten, nicht-obstruktiven Harnwegsinfektionen.

2. Säuglinge und Kinder, die in urologischer Hinsicht genau untersucht wurden und keine obstructiven Missbildungen aufwiesen, bilden

die Basis dieser Untersuchung über den Einfluss einer akuten Harnwegsinfektion auf die Funktion der Niere. Die Infektionen waren in allen Fällen leicht — vom Typ der oft klassifizierten Cystopyelitis.

Das Konzentrationsvermögen war in 17 Fällen subnormal. Die Dauer dieser funktionellen Störung war schwer genau zu bestimmen. In einigen Fällen dauerte sie möglicherweise 4-6 Wochen nach der Entfieberung. Die Urinbefunde waren in der Mehrzahl der Fälle normalisiert, während noch wahrscheinlich eine funktionelle Störung vorlag.

Die spezifische endogene Creatinin-Clearance, untersucht in 19 Fällen, war nur in 2 Fällen subnormal — die einzigen beiden mit einem starken beiderseitigen vesicoureteralen Rückfluss. In diesen beiden Fällen normalisierte sich die Creatinin-Clearance nach Behandlung der Infektion trotz weiterbestehenden Rückflusses. Die Bedeutung dieser Befunde wird besprochen. Die Creatinin-Clearance war in 3 Fällen nicht bestimmt worden.

Das Vermögen, Urin mit niedrigem pH auszuscheiden, wurde in 17 Fällen untersucht. Es war keine deutliche Schwäche festzustellen.

Die Untersuchungen zeigen, dass oft eine Beteiligung des Nierenparenchyms bei einer gewöhnlichen akuten Harnwegsinfektion vorliegt. Diese Tatsache stützt weiter die Auffassung, diese Infektionen mit hinreichend grossen Dosen chemotherapeutischer Substanzen zu behandeln, um eine genügend hohe Konzentration auch im Nierenparenchym zu erreichen. Die Dauer der Therapie wird mit Hinblick auf diese Ergebnisse diskutiert. Möglicherweise können diese Resultate die Auffassung stützen, diese Infektionen chemotherapeutisch mehrere Wochen nach Schwinden klinischer Zeichen und Symptome zu behandeln.

Estudio de la función renal en lactantes y niños con infecciones agudas no obstructivas del aparato urinario.

Para el desarrollo de esta investigación sobre la influencia de la infecciones agudas del tracto urinario sobre la función renal, se partió de un grupo de 22 lactantes y niños que luego de sometidos a un estudio completo desde el punto de vista urológico, demostraron no poseer malformación obstructiva alguna. Las infecciones han sido en todos los casos moderadas, del tipo a menudo clasificado como cistopielitis.

La capacidad de concentración fué hallada por debajo de lo normal en 17 casos. La duración de esta incapacidad funcional fué difícil de establecer. En algunos casos posiblemente se haya prolongado hasta 4-6 semanas luego de la caída de la fiebre. Los datos urinarios se presentaron normales en la mayoría de los casos cuando aún, probablemente, existía un déficit funcional.

El clearance de la verdadera creatinina endógena fué subnormal en solo 2 casos (los 2 únicos casos con reflujo bilateral véscicoureteral masivo). En ambos casos el C_{CR} se normalizó luego del tratamiento de la infección, pese a la persistencia del reflujo. La significación de estos hallazgos es discutida. El C_{CR} no fué investigado en 3 casos.

La capacidad de acidificación fué investigada

en 17 casos; sin que un déficit evidente pudiera ser exteriorizado.

La investigación muestra que existe a menudo un toque del parénquima renal en las infecciones agudas comunes del tracto urinario. La demostración de este hecho autoriza la opinión de que dichas infecciones deben ser tratadas con agendas quimioterápicas en dosis suficiente como para obtener altas concentraciones en el parénquima renal. La duración del tratamiento es discutida a la luz de estos hallazgos. Los resultados prestan apoyo, posiblemente, a la idea de que estas infecciones deberán ser tratadas quimioterápicamente durante varias semanas después de la desaparición de la sintomatología clínica.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

The Relation of Hyperbilirubinemia in Newborns without Isoimmunization to Kernicterus

by A. MORES, I. FARGAŠOVÁ and E. MINAŘÍKOVÁ

There appears to be no doubt about the fact that the high level of indirect bilirubin observed in the course of hemolytic disease of the newborn is perhaps the most important factor in determining the occurrence of kernicterus in newborn infants and that early exchange transfusion is the only effective prophylaxis of such an event. Experience has shown that in full-term infants the dangerous level lies between 20 and 25 mg % of bilirubin (26). In premature infants it has been found to be safer to perform exchange transfusion at a lower level (28).

However, even in so called physiologic jaundice of the newborn the level of indirect bilirubin may reach levels which in hemolytic disease of the newborn are certainly dangerous. While the level usually does not reach more than 10–12 mg % it may in some infants rise considerably above 20 mg % (7, 8, 10, 11, 38). When it was in retrospect recognized that even this “physiologic” jaundice may cause death or permanent disability many authors suggested the same treatment as in cases of severe jaundice resulting from hemolytic disease of the newborn, that is,

timely and adequate exchange transfusion.

This pathologic “physiologic” jaundice and the icterus from isoimmunization must be evaluated differently according to their occurrence in full-term or in premature infants, the course being usually more severe and more often fatal in the latter than in full-term infants. (1, 5, 13, 16, 19, 20). For this reason they will be discussed separately. From our experiences we shall try to answer the following questions:

1. What is the frequency of this pathologic “physiologic” jaundice in full-term and in premature infants and what are the values it may reach?
2. How often is the brain damaged in both groups?
3. Is exchange transfusion necessary to prevent it?

Technique

Determination of bilirubin was performed using Whit's modification of the Jendrassik-Grof method on a Pulfrich colorimeter (27). Bilirubin was determined as total bilirubin which corresponds approximately to the

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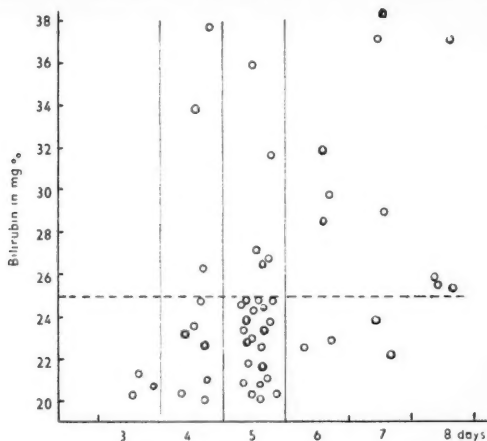


Fig. 1. The highest levels of bilirubin in 54 full term.

values of indirect bilirubin, because the amount of direct bilirubin is in most cases represented only by 0.5 to a maximum of 1.5 mg% of the total value of bilirubin. Blood was taken when icterus appeared in the course of the first 24 hours or even later if its intensity was higher than that usually found in cases of newborn icterus. In children showing 20 and more mg% of bilirubin repeated examinations were performed each or every second day as long as the level of bilirubin did not fall below 20 mg%. To exclude isoimmunization serologic examination was performed in all infants. The presence of Rh antibodies was looked for in the mothers and the direct Coombs' test performed in the children. In the ABO system the direct and indirect Coombs' test was performed to test the sensitivity of the child's erythrocytes and in the mother Witelsky's test and the hemolysin test were used. All patients were re-examined at about 6 months, and at one, two and four years of age. The psychosomatic development and the state of hearing, impairment of which may be the only sign of previous kernicterus, were followed.

A. Full-term infants

In the course of one year (from July 1953 to June 1957) some form of patho-

logic jaundice was seen in 48 full-term infants from a group of 2213 live births in the Maternity Hospital. These were either definitely positive cases of isoimmunization or only "physiologic" jaundice. The jaundice appeared in the course of the first 24 hours or later but the level of bilirubin was surprisingly high. There were 18 cases of jaundice resulting from isoimmunization due to Rh and ABO incompatibility and in 30 infants signs of isoimmunization were absent. In 12 of these infants the blood groups of mother and child were compatible with ABO immunization but there was no hemolysis. In 11 infants the jaundice started within 24 hours. Seven of these had a potentially incompatible ABO system and the bilirubin value in these reached 10.1 to 22 mg% with the maximum level occurring from the second to the fifth day. In the remaining 19 infants icterus began as late as on the second or the third day after birth. In 5 cases the blood group picture was ABO but the level of bilirubin was between 22 to 38 mg% and it reached its maximum between the 4th and the 9th

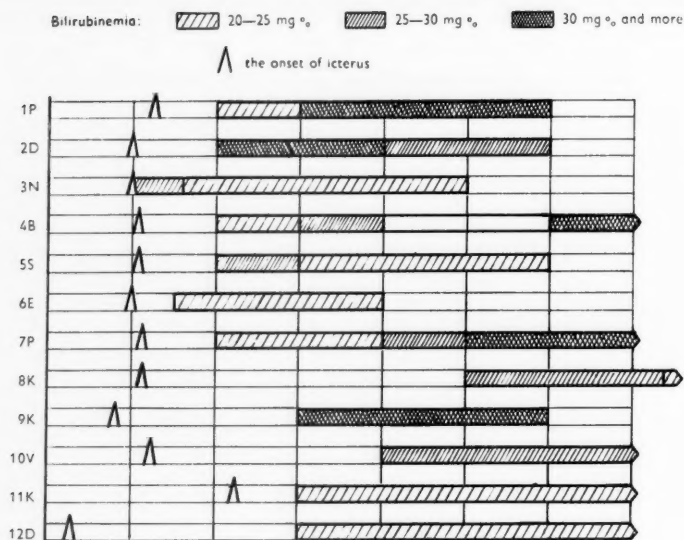


Fig. 2. Survey of duration of bilirubinemia in 12 full term.

day of life. On the whole, bilirubin reached values over 20 mg % in 22 infants (Fig. 1). In none of these infants was exchange transfusion performed and all of them are physically and mentally normal. At the Pediatric Clinic during a two years period (1955 and 1956) we have followed 32 other full-term infants coming from different maternity hospitals because of a bilirubin level over 20 mg % (Fig. 1). In 2 infants icterus appeared about 24th hours after birth, in 9 it appeared on the second day, in 14 on the third day, and in the rest on the fourth day. Serologic incompatibility was carefully eliminated. In ten infants the bilirubin level was higher than 25 mg %, in four it was as high as 30 mg %. Neither the time when the high levels were attained nor the period of their duration (in 12 infants it was 3 days and more, Fig. 2) influenced the health of

these infants and all remained quite normal.

B. Premature infants

We did not pay any attention to the question whether premature infants suffer from neonatal jaundice more frequently than full-term ones. During the two year period (1955–1956) in the Institute for Premature Infants we studied only those in whom more intensive visible icterus was present. Special attention was paid to the infants in whom the level of bilirubin was at least 15 mg %.

A total of 170 premature infants were studied. In 134 the level of bilirubin was higher than 15 mg % and in 70 of them it was higher than the safety limit generally accepted, i.e. 20 mg % (Table 1). Clinically the jaundice was visible on the third or fourth day in 80 % of the infants and

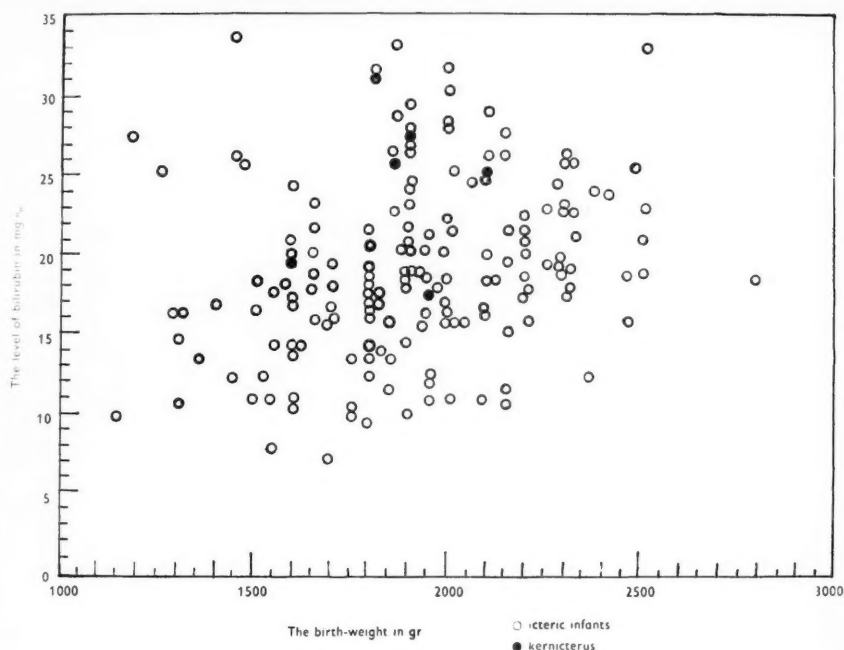


Fig. 3. The relation of the level of bilirubin to the birth-weight in 170.

TABLE 1. *The highest level of serum bilirubin in 170 premature infants.*

The level of bilirubin in mg %	Number of infants	%
0-10	5	2.9
10-15	31	18.3
15-20	64	37.6
20-25	40	23.6
25-30	23	13.5
30-35	7	4.1
Total	170	100.0

TABLE 2. *The onset of jaundice.*

Day of the onset	Number of infants	%
2nd day	21	12.4
3rd "	93	54.7
4th "	43	25.3
5th "	13	7.6
Total	170	100.0

Duration of jaundice.

Duration	Number of infants	%
1 week	64	37.6
2 weeks	68	40.0
3 "	36	21.2
4 "	2	1.2
Total	170	100.0

lasted from one to three weeks (Table 2). In none of our cases was the jaundice visible in the first 24 hours or at least it did not appear to be sufficient enough to be clinically evident. No relation be-

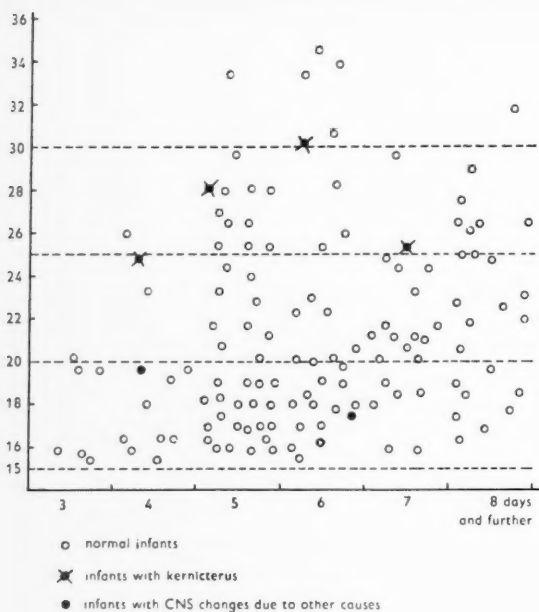


Fig. 4. The maximal levels of bilirubin.

tween the level of bilirubinemia and the birth-weight has been observed (Fig. 3), but a certain distortion in the range of the lowest weights may be due to the small number of examined infants. The time when maximal values of bilirubin greater than 15 mg % were recorded is shown in Fig. 4.

Seventeen infants died (3 in the neonatal period, 14 between 1 and 18 months). The 153 infants who survived were examined between 3 months and 4 years of age. Eighteen of them at 4 years of age, 20 at 3 years, 10 at 2 years, 36 at about 1 year, 19 at 6 months and 11 at about 3 months of age. Out of 70 infants with the level of bilirubinemia more than 20 mg % 11 died and 53 were followed up; 16 of them at 4 years, 20 at 3 years, 9 at 2 years, 2 at 1 year, 2 at 6 months and 4 at 3

month of age. No signs of neurological abnormality were visible at this time.

Damage of the central nervous system of various degrees was found only in 6 infants (Table 3). One of them died in the neonatal period (D.I.) with evident clinical, anatomical and histological signs of kernicterus. Three other infants (P.V., Č.P., K.V.) died between the age of 3 to 18 months. All these infants had quite clear clinical signs of central nervous system changes which could not be explained other than by severe jaundice. In patient P.V. this reached 31.3 mg % of bilirubin on the 6th day and remained at this level for four days, in the other two patients it reached 24.9 mg and 25.4 mg % and their condition deteriorated with the continuance of jaundice, i.e. they drunk badly and were very sleepy. Post mortem exami-

TABLE 3. *The level of serum bilirubin in 6 premature infants with CNS changes.*

Infant	Birth-weight	The highest level of bilirubinemia in mg %		Jaundice		Blood group		Note
				Onset	Duration	Mother	Infant	
P.V. ♂	1820 g	On the						
		6th day	31.3	3rd day	3 weeks	O +	B +	died
H.P. ♂	1600 g	4th "	10.6	3rd "	4 "	O -	A +	
Č.B. ♀	1950 g	6th "	17.5	2nd "	2 "	O +	O +	
Č.P. ♂	1880 g	7th "	25.4	3rd "	2 "	O +	O +	died
K.V. ♂	2100 g	4th "	24.9	2nd "	4 "	O +	O +	died
D.I. ♂	1900 g	5th "	28.1	3rd "	died 8th day	AB +	B +	exsang. Kern- icterus

nation was performed only in one of the last 3 infants at the age of 3 months (P.V.) but, of course, the brain no longer showed the characteristic changes caused by kernicterus. In this infant as in the case of an other living one (H.P.) isoimmunization in the ABO system could not be excluded because of imperfect serologic and hematologic examinations. However, it is not

probable because the jaundice in both infants did not appear before the third day of life and they showed no signs of anemia. Furthermore, in the appearance of the central nervous system alteration anoxia could have participated as a result of neonatal bronchopneumonia in the first infant. In the second infant showing a level of bilirubin of 19.6 mg % severe as-

TABLE 4. *Infants with high bilirubinemia developing normally.*

Infant	Birth-weight	The highest level of bilirubinemia in mg %		Jaundice		Follow-up at the age of
				Onset	Duration	
Šp. ♀	1400 g	33.9		3rd day	11 days	2 1/4 years
N. ♀	2500 g	33.4		4th "	16 "	3 "
St. ♀	1850 g	33.4		3rd "	21 "	3 "
Z. ♀	1800 g	31.8		3rd "	25 "	4 "
P. ♂	2000 g	30.7		3rd "	15 "	3 1/2 "
H. ♂	1900 g	29.7		2nd "	16 "	3 "
M. ♂	2100 g	29.7		4th "	10 "	2 "
L. ♀	2000 g	28.3		3rd "	16 "	3 1/4 "
S. ♀	1900 g	28.1		3rd "	14 "	3 "
Š. ♀	2150 g	28.0		?	17 "	3 1/2 "
Li. ♀	2000 g	28.0		3rd "	19 "	3 1/4 "
Hr. ♀	1200 g	27.6		3rd "	18 "	4 "
Sk. ♀	1900 g	27.0		3rd "	21 "	2 1/4 "
Č. ♀	1850 g	26.5		4th "	23 "	1 1/2 "
K. ♀	2100 g	26.5		2nd "	16 "	2 1/4 "
R. ♀	1970 g	26.5		3rd "	19 "	3 1/4 "
F. ♂	2300 g	26.0		3rd "	10 "	2 1/4 "
G. ♀	2470 g	25.4		3rd "	12 "	4 "
Če. ♀	1470 g	25.4		3rd "	10 "	3 1/4 "
Sm. ♀	1250 g	25.4		2nd "	21 "	3 "

TABLE 5. *Causes of death in premature infants with high bilirubinemia.*

Infant	Age	The highest level of bilirubin in mg %	Causes of death	Kernicterus symptoms	
				clinical	post mortem
La. ♂	6 days	32.0	pneumonia interstitialis	—	—
D. ♂	8 "	28.1	icterus nuclearis	+	+
H. ♂	14 "	26.5	sepsis umbilicalis	—	—
P. ♂	1 month	24.4	pneumonia interstitialis	—	—
K. ♀	2 "	24.0	pneumocystis Carini	—	—
R. ♀	3 "	18.0	pneumocystis Carini	—	—
Č. ♀	3 "	29.0	pneumocystis Carini	—	—
J. ♀	4 "	15.9	bronchopneumonia abscedens	—	—
Př. ♂	4 "	31.3	pneumocystis Carini	+	—
Pa. ♂	7 "	18.0	pneumonia interstitialis	—	—
T. ♀	10 "	20.1	fibroelastosis atrii sin.	—	—
S. ♂	15 "	23.3	meningitis purulenta	—	—
Č. ♂	12 " (after)	25.4	section not performed	+	?
L. ♂	14 "	20.1	meningitis pneumococcia	—	—
Ko. ♂	18 "	24.9	section not performed	+	?

phyxial attacks were observed immediately after birth probably caused by traumatic injuries. In the infant Č.B. a birth injury was very probably present as well. After a difficult birth there remained quadriparesis and other signs of birth injury. Jaundice reaching only 17.5 mg % of bilirubin probably did not make the conditions worse anyhow.

If we do not count these two last infants in whom the disease was caused rather by birth trauma than by jaundice there were only 4 infants suffering from kernicterus out of the entire 170 icteric premature infants that were studied, i.e. 2.3 %. These all had a level of bilirubin of 25 mg % and more but the other 27 infants who were exposed to equally high bilirubinemia are at follow-up between 2 and 4 years of age quite healthy (Table 4).

Out of the 17 premature infants who died at different ages, i.e. 3 in the neonatal period and the others between 1 and 18 month the level of bilirubin was higher than 15 mg % in 15 infants (Table 5).

Kernicterus was the cause of death only in one infant, whose level of bilirubin was 28.1 mg %. Out of three infants shown in Table 3 as damaged in the central nervous system (K.V., Č.P., P.V) autopsy was performed only in one (P.V.), at the age of 4 months. The cause of death was bronchopneumonia and no direct evidence of kernicterus were found.

Discussion

The high number of full-term infants with hyperbilirubinemia without isoimmunization cannot be explained by any apparent or supposed pathologic process. No drugs were administered to these infants, all were in good somatic condition: they drank well and gained well in weight. Not one infant, even from among those with a bilirubin level over 30 mg % showed any signs of CNS damage though in none was exchange transfusion performed. This experience has resulted in some, though only a relative, amount of security: that

a full-term infant in whom isoimmunization can be ruled out, needs no form of treatment even if the attained level of bilirubin is higher than 25 mg %.

Because only 4 infants compared to the remaining 27 undamaged premature infants with equally high bilirubinemia of 25 mg % and more (Fig. 3) were damaged we may suppose that bilirubinemia alone was not the decisive factor in the kernicterus. Its relatively low frequency (i.e. 13 %) is contrasted with our experience with the same hyperbilirubinemia in hemolytic disease of the newborn from incompatibility of Rh or ABO where kernicterus was observed nearly in 30 %. It is very probable that more infants escaped the same fate only by adequate and timely treatment (26). Comparing only the premature infants with hemolytic disease of the newborn with bilirubin levels over 25 mg % then 60 % of the infants with isoimmunization suffered damage (16). Exchange transfusion in these infants was either not performed or performed too late.

The cause of this evidently different reaction of the infants to the two types of bilirubinemia cannot be looked simply in the hyperbilirubinemia even if there were only premature infants concerned. Imperfect or selectively disturbed liver function, as suggested by many authors, disorders of carbohydrate metabolism (4), birth trauma or anoxia (15, 18), or on the contrary the surplus of oxygen (3, 13), infection (31, 35, 39), insufficient nutrition of mothers (39), or vitamin K (6, 22, 33, 40) and gantrisin (8, 35), all these are factors which cannot be ignored in planning efficient prevention.

The existence of kernicterus without isoimmunization in full-term infants can-

not be denied but it has been found very rarely. Also the maturity of some of the reported infants can be questioned because their birth-weight was below 3000 g (1, 5, 13, 15, 34, 39). It is possible that at least some of them belonged in the premature group, though they had not the visible signs of prematurity, especially if the dates of the duration of pregnancy were missing. But it seems certain that some of the above mentioned were really full-term infants and it is necessary to consider if by timely performed exchange transfusion it would have been possible to prevent kernicterus.

Only two authors are convinced of the necessity of exchange transfusion in full-term infants and have also performed it, when the level of bilirubin reaches over 20 mg % (10, 17). We did not in any way treat our 54 infants with hyperbilirubinemia of 20 mg % and more and all of them are getting on quite well. As we can see in Fig. 1 many of the infants had a level of bilirubin of 25 mg % and more and even without exchange transfusion no kernicterus developed in them. Based on this experience we now suppose that it is useless to perform an exchange transfusion on full-term infants with intensive jaundice without isoimmunization because these infants are neither in danger, nor ill; they are only icteric.

The existence of kernicterus in premature infants without isoimmunization is well known but reports of its frequency differ greatly. In our material it occurs in less than one per cent because among 420 prematurely born and surviving infants it was diagnosed in four cases and among 250 infants liveborn but dying within ten days of age it was diagnosed at autopsy

only in two cases. Other authors have stated that the frequency of kernicterus in these infants is far greater: it has been said to occur in 2-3 % of all post mortem examined premature infants (12, 14, 15, 23, 30) and also 15 % (32), 16.6 % (1), 21 % (36), 30 % (24), 50 % (3), (25) and Meyer claims 60 % kernicterus in all premature infants whose level of bilirubin was higher than 18 mg %. The explanation of these so striking differences is very difficult. Even if it might be suggested that some hospitals do not use the correct criteria for evaluation of changes in the brain it is also possible that other factors take part in the relation of excessive hyperbilirubinemia and kernicterus in premature infants, such as technique of birth and the nursing of the newborn, drugs and other previously mentioned circumstances. Also local conditions perhaps only temporary but not well known till now, are excluded (3). In Prague, in the Institute for Mother and Child hyperbilirubinemia over 20 mg % without isoimmunization has been found only quite rarely. On the contrary it was found quite often by Bowman but was not associated with kernicterus (7, 8).

If the existence of kernicterus without isoimmunization in premature infants seems to be proven, then it is necessary to consider the possibility of its prophylaxis. Our infants with high bilirubinemia without any disturbances as Bowman's with bilirubin of 20-27 mg % (7, 8), Bruck's with 32-38 mg % (11) and those of News' *et al.* with 20-28 mg % of bilirubin (27) stand against the opinion that kernicterus is due only to the indirect bilirubin resulting from lysis of erythrocytes of the newborn. Neither do we know anything of prematurity or disturbance

of liver function which are the second supposed cause of hyperbilirubinemia, except that under some conditions they are not able to transfer by some mechanism the indirect and sometimes toxic bilirubin to nontoxic direct bilirubin. Some authors think that the defective carbohydrate metabolism together with insufficient conjugation of bilirubin with glucuronic acid may be responsible (4). Other authors suppose insufficiency of enzyme mechanisms (9, 15). Therefore, the indications for exchange transfusion are perhaps different from hemolytic disease of the newborn and this way of preventing of kernicterus from mere hyperbilirubinemia has not been sufficiently theoretically proven. But many workers are performing exchange transfusion some of them at a bilirubinemia of 18 mg % (3), others over 20 mg % (10, 17, 37) or more than 30 mg % (27) and some are performing it as late as when the first symptoms of the alteration in the CNS occur (3). We did not perform any exchange transfusion in any observed premature infant with hyperbilirubinemia without isoimmunization and in spite of this we have seen kernicterus only in one percent of them. It is not probable that a better result could be obtained by exchange transfusion because this procedure in premature infants is not without danger.

Conclusions

1. Hyperbilirubinemia without isoimmunization in full-term and especially in premature infants is more frequent than hyperbilirubinemia from isoimmunization. Its height may even equal the latter, however, the maximum level is usually reached as late as the 5th day and later.

2. Damage to the central nervous system from this hyperbilirubinemia has not been found in full-term infants. The number of cases of kernicterus in living premature infants or in cases from post mortem material has not exceeded 1%.

3. Prophylactic exchange transfusion in full-term infants is useless, in premature infants it is theoretically unfounded and its practical value has not been proven, not even by those performing it.

Thus, if we are able to exclude isoimmunization as a cause of hyperbilirubinemia and this is nearly always possible after careful clinical, hematologic and serologic examination, we may allow it to follow its natural course.

Summary

When studying the level of hyperbilirubinemia without isoimmunization we found that on the whole in 54 full-term infants it had reached a level of over 20 mg %, in 19 of them over 25 mg % and in 9 even over 30 mg %. Neither the time of attainment of this hyperbilirubinemia nor its duration have influenced the health

of the infants, and all of them are getting on quite well. Among the 170 intensive-ly icteric premature infants with hyperbilirubinemia over 15 mg % only 4 were affected by kernicterus, i.e. 2.3%. The level of bilirubin in these four infants reached over 25 mg % but it had been the same in 27 infants of equal weight and these remained healthy. Among these 170 premature infants the level of bilirubin reached 15 mg % and more in 134 infants, in 70 of them it reached over 20 mg % and in 31 even 25 mg %. The frequency of kernicterus among live born premature infants and its part in the mortality of newborn premature infants was less than 1%. Possible causes of hyperbilirubinemia are discussed but from our experience we suppose that hyperbilirubinemia itself, without isoimmunization is not, even in premature infants, the main and only cause of kernicterus. Therefore, we do not perform exchange transfusion in full-term as well as in premature infants with high bilirubinemia if we are able to exclude that it is not caused by some isoimmunization.

Relation entre l'hyperbilirubinémie sans iso-immunisation et l'ictère nucléaire chez le nouveau-né.

En étudiant le taux de l'hyperbilirubinémie sans iso-immunisation, nous avons constaté que pour un ensemble de 54 bébés nés à terme, ce taux avait dépassé le niveau de 20 mg % et qu'il était notamment supérieur à 25 mg % chez 19 d'entre eux et même à 30 mg % chez 9 autres. L'époque à laquelle ce taux d'hyperbilirubinémie a été atteint de même que la durée de la période depuis laquelle il existait n'ont eu aucune influence sur la santé de ces bébés qui sont tous très bien portants. Sur les 170 bébés prématurés atteints d'ictère avec une hyperbilirubinémie de plus de 15 mg %, 4 seulement ont été victimes d'un ictère nucléaire, ce qui représente une proportion de 2,3 %. Le taux de la bilirubine chez ces 4 enfants dépassait 25 mg %, mais il y a lieu de noter que des taux analogues ont été

relevés chez 27 autres bébés de même poids qui sont restés bien portants. Les taux de bilirubine relevés chez ces 170 nourrissons furent de 15 mg % et plus dans 134 cas, de 20 mg % et plus dans 70 cas et même de 25 mg % et plus dans 31 cas. La fréquence des cas d'ictère nucléaire chez les enfants prématurés nés vivants et la part qu'ils ont prise dans la mortalité des nouveau-nés prématurés ont été inférieures à 1 %. Les différentes causes possibles de l'hyperbilirubinémie sont passées en revue mais, d'après notre expérience, nous pensons qu'en elle-même, l'hyperbilirubinémie sans iso-immunisation n'est pas, même chez les prématurés, la principale ni la seule cause de l'ictère nucléaire. C'est pourquoi nous ne pratiquons pas de transfusions d'échange chez les enfants nés à terme ni chez les prématurés présentant une bilirubinémie élevée si nous sommes en mesure d'exclure que cette dernière soit due à une iso-immunisation.

Das Verhältnis der Hyperbilirubinämie der Neugeborenen ohne Isoimmunisierung zum Kernikterus.

Beim Studium des Hyperbilirubinämiespiegels ohne Isoimmunisierung fanden wir, das derselbe bei 54 vollzeitig Geborenen im ganzen mehr als 20 mg % erreicht hatte, bei 19 unter ihnen 25 mg % und bei 9 unter ihnen sogar 30 mg % überstieg. Weder der Zeitpunkt der Erlangung dieser Hyperbilirubinämie noch ihre Dauer beeinflussten das Wohlbefinden dieser Kinder und alle machten gute Fortschritte. Unter den 170 stark gelbsüchtigen Frühgeborenen mit Hyperbilirubinämie über 15 mg % hatten nur 4, d.h. 2,3 % Kernikterus. Der Bilirubinspiegel bei diesen Kindern erreichte über 25 mg %, aber dasselbe war der Fall bei 27 Kindern von gleichem Gewicht und diese waren gesund geblieben. Unter diesen 170 Frühgeburten erreichte der Bilirubinspiegel 15 mg % und darüber bei 134; bei 70 von diesen erreichte er 20 mg % und bei 31 sogar 25 mg %. Die Häufigkeit von Kernikterus unter lebend geborenen vorzeitigen Kindern und sein Anteil bei der Sterblichkeit von neugeborenen Frühgeburten betrug weniger als 1 %. Die möglichen Ursachen der Hyperbilirubinämie werden diskutiert; die Verfasser nehmen an, dass Hyperbilirubinämie allein ohne Isoimmunisierung selbst bei Frühgeburten nicht die hauptsächlichste und ausschliessliche Ursache des Kernikterus ist. Deshalb wird weder bei vollreifen noch bei vorzeitigen Kindern mit hoher Bilirubinämie eine Austauschtransfusion ausgeführt, wenn irgendeine Form von Isoimmunisierung als kausale Ursache ausgeschlossen werden kann.

Addendum

To ascertain the accuracy of our conclusions a follow-up examination of 45 premature infants with bilirubinemia over 20 mg % without isoimmunization in the neonatal period was repeated one year after completing this paper. Three of them died but they had neither symptoms of damage of the CNS while alive, nor were there found any indirect signs of kernicterus at post mortem examination. In the living ones there are the signs of CNS

La relación de la hiperbilirrubinemia en recién nacidos sin isoimmunización al Kernikterus (icticia nuclear).

Al estudiar el nivel de la hiperbilirrubinemia sin isoimmunización hallamos que en 54 niños a término había alcanzado más de 20 mg %, en 19 de ellos más de 25 mg % y en 9 incluso pasaba de 30 mg %. Ni la época en que se alcanzó esta hiperbilirrubinemia ni su duración influenciaron el estado de los niños, y todos ellos siguen bien. De los 170 niños prematuros intensamente ictericos con hiperbilirrubinemia superior a 15 mg %, solo 4 aquejaron una ictericia nuclear, es decir, el 2,3 %. El nivel de bilirrubina en estos cuatro niños sobrepasó los 25 mg % aunque fue el mismo que en 27 niños de igual peso, sanos. De estos 170 niños prematuros el nivel de bilirrubina alcanzó 17 mg % o más en 134 niños, en 70 de ellos sobrepasó los 20 mg % y en 31 incluso los 25 mg %. La frecuencia del kernikterus entre los niños prematuros vivos y su participación en la mortalidad de los niños prematuros recién nacidos fue menor del 1 %. Se discuten las causas posibles de la hiperbilirrubinemia, pero en función de nuestra experiencia suponemos que la hiperbilirrubinemia misma, sin isoimmunización no es la única y primordial del kernikterus, aun en los prematuros. Así pues no efectuamos exsanguinotransfusiones en los niños prematuros con bilirrubinemia elevada si podemos excluir que no se debe a alguna isoimmunización.

damage in one infant that was probably due to birth-trauma (at the time of the first follow-up examination he was 6 months old and seemed to be normal), because there was large cephalhematoma. Eight infants have simple speech retardation but they are otherwise normal with good-hearing. The other 33 are developing quite normally physically and mentally. All infants at this follow-up were 2-4 years of age.

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Pediatric Clinic
Palackého University
Olomouc
Czechoslovakia

Membranous Stomatitis

by PER SELANDER

In 1948 Faucett & Miller reported that during a period of $2\frac{1}{2}$ years they had observed 6 children, aged from 5 days to 27 months, who exhibited a stomatitis. The children had pains in the mouth, screamed and refused to eat. There was no fever, the white blood cell count was normal, and the children did not appear to be generally affected. The stomatitis could be differentiated from thrush by a greater tendency to confluency and a heavier, dirtier-appearing membrane. A gram-negative organism belonging to the *Bacillus mucosus capsulatus* (Friedländer) group could be cultured from all the patients. In 1060 controls this bacillus was found only once. In 1956 Sternberg, Hoffman & Zweifler described a seventh case, an immature baby, who on the eleventh day of life developed dyspepsia and at the same time exhibited a stomatitis that was characterized by a dirty, white, firmly adherent membrane on the buccal mucosa, hard palate and tongue. Cultures of the stools and from the mouth yielded a bacillus belonging to the *Bacillus mucosus capsulatus* group.

To my knowledge there are no other reports of membranous stomatitis in in-

fants in the literature. Since also the handbooks do not mention this condition, I consider it of value to communicate our experiences of this, especially for the neonatal period, characteristic disease.

Occurrence. Prior to 1957 no case had been observed at the Children's Hospital in Malmö. In June 1957 one case was admitted; since then a total of 43 cases have been treated. I have received reports of further 6 cases from doctors and nurses of the Child Health Centers in the city. All infants were born in the Maternity Hospital in Malmö, and the frequency of the infants in the 5 nurseries has been the following:

Nursery	No. of infants	No. with membranous stomatitis
AB	2,258	23 (10 p.m.)
BA	2,436	22 (9 p.m.)
A, P, S	1,352	4 (3 p.m.)

Age, sex and weight. Of the 49 infants 8 became sick during the first week of life, 21 in the second and 9 in the third. The two youngest were 3 and 4 days old; the two oldest 40 and 49 days old. All were taken sick after having been discharged from the Maternity Hospital.



Fig. 1. Membranous stomatitis. Typical appearance with membrane on the tongue.



Fig. 2. Membranous stomatitis. Disappearing membrane.

Twenty-four were boys and 25 girls. Two were immature babies, the smallest weighed at birth 1480 g, the biggest weighed 4180 g.

Feeding. Thirty-three of the children were only breast-fed, 11 were breast- and bottle-fed and 5 were only bottle-fed at the onset of the disease.

Clinical symptoms. The symptoms have been the following. One day the infant refused to eat or rather was unable to eat, he tried to suck but his attempts were interrupted by screaming. Examination has usually revealed a grayish white, sharply limited membrane, most often on the tongue, but frequently also on the hard palate. Some infants on the first examination have exhibited a reddened tongue with an uneven thin coating, and

we have seen some cases with blisters resembling neonatal pemphigus on the tongue and hard palate. Characteristic of the condition are the grayish white, sharply limited membranes, which pass over into normal mucous membrane without any signs of inflammation in the tissue surrounding the membrane (Fig. 1 and 2). It is typical that the membrane gives the impression of being strongly adherent, it seems to be a part of the mucous membrane. But it can be easily detached, however, and leaves then a slightly bleeding sore surface. It has happened that the membrane has become unattached by itself. After having become unattached or having been freed it can be reformed already within 24 hours, but then it is not so imposing.

One may also find several membranes at the same time, e.g., two on the tongue, one membrane on the tongue and one on the hard palate.

The reddened mucous membrane and the thin coating give the impression of acute infection and should be the initial stage; the same is the case with the blister formation. This stage passes over rapidly, and we have observed even in early cases these above-described well-limited membranes.

The general condition is unaffected, only one infant has had fever (at the same time otitis), the sedimentation rate is most frequently normal, the white blood cell count is not increased.

Course. The oral changes culminate after a couple of days, then remain unchanged for some days and thereafter begin to disappear slowly. Complete recovery in most cases has taken place within two weeks. In a weak immature infant, however, the changes lasted for 35 days. No relapses have occurred.

Etiology. Bacteriologic examinations of 33 infants have been carried out at the Bacteriological Institute of Malmö General Hospital (Winblad). Specimens have been taken from scrapings of the membrane, from blisters in the mouth, in some cases also from the feces, and in some cases we have also made cultures directly from the detached membrane. The bacterial flora has always been the same as that found in normal children. Almost all infants have exhibited staphylococcus aureus; these have been of the common mesocomial strains occurring saprophytically in the infant oral cavity. They belong to different phage groups, and this makes it less probable that they have any

etiologic significance in the occurrence of the markedly uniform syndrome. In no case has it been possible to culture bacilli belonging to the Friedländer group, despite the fact that the investigations have been concentrated on this group. Examinations for spirochetes, monilia and virus have likewise been negative.

Attempts have also been made to inoculate the stomatitis. Scrapings from membranes have been transferred to 9 infants aged 3 to 18 days. In one case a severe stomatitis developed on the tenth day following inoculation. This child, who was in a hopeless condition, died on the thirteenth day after inoculation from his primary disease; he did not exhibit any membranes, but it was obviously a question of an atypical and severe stomatitis. Another infant developed on the fourth day after inoculation a moderately severe moniliosis, which however did not resemble at all the primary stomatitis. In other cases no reaction was obtained.

Histology. Microscopic examination has revealed that the membrane is composed of leucocyte-filled fibrin. Examination of the tongue of the inoculated infant showed that the surface was covered with a "regular squamous epithelium, which for the most part was highly differentiated but in places there was a suggestion of atypia with quite a few mitoses. Subepithelially a sparse storage of round cells was seen. Within some isolated smaller regions the epithelium was partly eroded, loose and exhibited accumulation of inflammatory cells. Subepithelially there was here an accumulation of polymorphonuclear leucocytes and some round cells" (F. Bergman).

Prognosis. The prognosis in all our

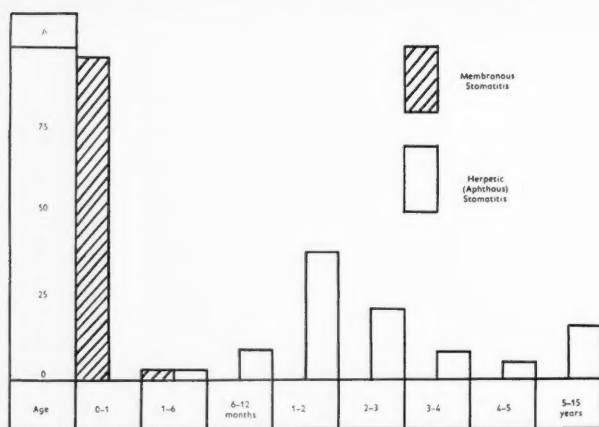


Fig. 3. The age of 49 children with membranous stomatitis and of 370 with herpetic stomatitis.

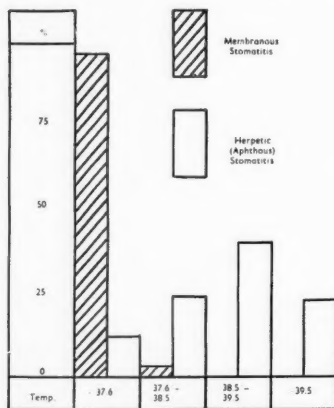


Fig. 4. The temperature of 42 children with membranous stomatitis and of 339 with herpetic stomatitis.

spontaneously occurring cases has been good. The infants appear to be troubled by the disease only during the first 2 to 3 days; later they eat normally, even if the membranes remain largely unchanged.

Treatment. The disease has not required any special treatment. Gentian violet (methyl rosanilin) has no effect, probably neither sulfa nor antibiotics which have been administered in several cases. The

disease follows its course regardless of what one does.

Discussion. The disease described here seems to be unknown in European literature. There has been no certain case in Malmö for the past 30 years or so. During the most recent years sporadic cases have occurred in southern Sweden. In Malmö no less than 49 cases have been observed in about 2 years.

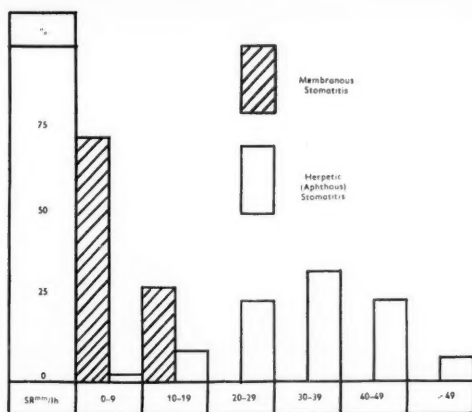


Fig. 5. The sedimentation rate of 37 children with membranous stomatitis and of 341 with herpetic stomatitis.

The disease is certainly not connected with irritating chemicals. The only conceivable ones at this age are from pacifiers or from the ointment from the mother's nipples. Both can be eliminated, since most of the affected infants have not used pacifiers and since the disease is cured in spite of the fact that the mother continues with the same pacifier and with the same nipple ointment.

It is obvious that the disease is neither connected with thrush; clinically they are dissimilar and gentian violet has no effect on the membranous stomatitis. Nor does it resemble herpetic (aphthous) stomatitis. As is seen from Fig. 3, herpetic stomatitis occurs in Malmö in another age than the membranous; herpetic stomatitis is often attended with fever (Fig. 4) and the sedimentation rate is almost always elevated (Fig. 5).

Most remarkable is the connection between *B. mucosus capsulatus* and membranous stomatitis which has been

found in the United States and the absence of this bacillar type among our cases. It is uncertain how this is to be explained.

It is probable that it is a question of an infection, since the disease appears to be transferable. Since no definitely pathogenic bacteria can be found, it may be assumed that it is caused by a virus. So far current investigations have not revealed, however, any particular virus.

Summary

Forty-nine cases of a hitherto seldom observed disease, especially in very young infants, are described. It is characterized by fibrin membranes, particularly on the tongue. The disease appears to be transferable, although the disposition towards the infection is slight, and the period of incubation in one case was 10 days. Therefore it is probably a question of an infection, but no definite bacteria or virus have been detectable.

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Flensburg Children's Hospital
Malmö
Sweden

From the Department of Obstetrics and Gynecology and the Chemical Central Laboratory, Sabbatsbergs sjukhus, and the Wenner-Gren Research Laboratory, Nortulls sjukhus, Stockholm, Sweden

Some Constituents of Umbilical Venous Blood of Previa Human Fetuses¹

by B. WESTIN, I. H. KAISER², J. LIND, R. NYBERG
and A. C. TEGER-NILSSON

Despite the increasing interest in studies of the previable human fetus, information about the physiologic concentrations of ordinary blood constituents is still meager, with the exception of a limited number of determinations of hemoglobin, hematocrit, red blood cell count and plasma proteins.

Measurements of hemoglobin, hematocrit, mean corpuscular hemoglobin concentration (MCHC) in the blood, and sodium, potassium, calcium and total and fractional protein concentrations in the plasma of a small number of living human fetuses ranging in weight from 50 to 750 g, are therefore reported below as a preliminary survey. In general, the values indicate several specific differences between the previable human fetus and the infant at term.

Material and Methods

The fetuses, with the exception of a few of the larger ones, were delivered by legal abortion on apparently physically healthy individuals. As soon as possible blood was drawn from the umbilical vein into a syringe

moistened with heparin solution. The fetuses were then weighed. For electrolyte determinations plasma was obtained by centrifugation of the blood within about one hour after drawing the sample.

Hemoglobin was determined as cyanmethemoglobin by means of a Beckman C photometer (Drabkin & Austin 1932 and 1935). Standard deviation was 1.1 per cent.

Hematocrit was determined according to Norberg & Warvenius and the standard deviation was 0.5 per cent.

Sodium and potassium were determined with the EEL flame photometer. The standard deviation was 4 per cent for potassium and 3 per cent for sodium. For potassium analysis all samples with visible hemolysis were excluded. To check the influence of potassium leakage from the red corpuscles, blood was withdrawn from the umbilical vein by means of plastic tubing into silicone-coated test tubes. After varying times (15 min–5 h) samples were centrifuged and potassium and hemoglobin determined in the plasma.

There was no significant increase in potassium concentration with time, but the small fluctuations paralleled the hemolysis.

Calcium was measured according to Kramer & Tisdall and the standard deviation was 1 per cent.

Total plasma proteins were determined after precipitation with 0.25-N trichloroacetic acid. The precipitate was digested with con-

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² Present address: Dept. of Obst. and Gyn., University of Minnesota, U.S.A.

TABLE 1. Hemoglobin, hematocrit and mean corpuscular hemoglobin concentration (MCHC) in heparinized umbilical vein blood of human fetuses.

Fetal weight in g	Hemoglobin (g/100 ml)			Hematocrit (vol %)			M.C.H.C.			n
	mean	range	n	mean	range	n	mean	range		
50-149	10.2	7.8-12.5	5	37.1	34.5-40.0	3	31.3	30.0-33.0		3
150-249	11.2	8.9-12.7	5	36.5	28.5-42.4	4	30.9	30.0-31.6		4
250-349	10.9	9.3-13.4	3	39.7	27.8-52.5	5	33.7	31.0-36.0		3
350-449	9.0	—	1	31.3	—	1	29.0	—		1
450-549	12.9	11.6-14.2	3	37.3	37.3-40.9	2	31.3	31.1-31.5		2
550-649	13.3	11.1-15.4	2	43.4	36.6-50.2	2	31.0	31.0-31.0		2
650-749	14.1	12.9-15.2	2	44.6	40.9-48.4	2	31.5	31.0-32.0		2

centrated H_2SO_4 and H_2O_2 at 270° for about 15 h. The ammonia liberated after alkalisation was determined after diffusion according to Conway.—The standard deviation was 1.8 per cent.

The different protein fractions were determined by paper electrophoresis in a K6iv-apparatus with a veronal buffer solution pH 8.6 and ionic strength 0.1 (K6iv, Wallenius & Gr6nvall). The strips were stained in Amido-Black and the different fractions were cut out and eluted and the absorbance at 635 $m\mu$ was measured in a Beckman B spectrophotometer. Normal values for adults by this method:

Albumin, mean value 80.5 per cent (range 60.1-90.0) per cent

Globulin { α_1 , mean value 4.1 per cent (range 1.4-4.6 per cent),
 α_2 , mean value 3.5 per cent (range 2.9-8.1 per cent),
 β , mean value 9.9 per cent (range 5.2-12.0 per cent),
 γ , mean value 6.4 per cent (range 5.8-16.2 per cent).

Results

In Table 1, the known trend toward increase in the hemoglobin concentration as fetal weight increases in this range can be seen. Although the small size of the series of the cases apparently obscures the increase in hematocrit, it will be noted that the mean corpuscular hemoglobin concentration (MCHC) remains unchanged. There are therefore larger numbers of red blood cells present, rather than an increased concentration of hemoglobin in each red blood cell.

The concentration of *potassium* in this entire group of fetuses is quite high (Table 2) and there is no evidence of a trend downward toward the normal levels at term. Hemolysis does not account for these values. *Sodium* concentrations are also generally elevated, although the distribution here is over a greater range, and

TABLE 2. Potassium, sodium and calcium concentrations in human fetal plasma.

Fetal weight in g	K ⁺ (meq/L)			Na ⁺ (meq/L)			Ca ⁺⁺ (meq/L)			n
	mean	range	n	mean	range	n	mean	range		
50-149	10.1	8.0-12.8	3	162	135-188	4	4.7	3.1-6.3		2
150-249	8.5	7.5-9.6	4	149	134-178	5	5.7	—		1
250-349	8.3	7.7-8.8	2	152	146-157	2	5.0	4.9-5.2		2
350-449	—	—	—	177	—	1	—	—		—
450-549	10.0	9.6-10.4	2	154	148-165	3	4.8	4.4-5.4		3
550-649	9.6	—	1	150	137-163	2	—	—		—
650-749	7.6	6.3-8.8	2	140	139-140	2	4.5	—		1

TABLE 3. *Plasma proteins in human fetal blood.*

Fetal weight in g	Total plasma proteins (g/100 ml)			Albumin fraction (g/100 ml)			Globulin fraction (g/100 ml)		
	mean	range	n	mean	range	n	mean	range	n
50-149	2.5	1.9-3.4	5	2.0	1.5-2.8	5	0.46	0.31-0.62	5
150-249	2.5	2.3-2.6	2	1.6	1.2-2.0	2	0.91	0.38-1.43	2
250-349	2.8	2.2-3.1	3	2.3	2.0-2.6	3	0.44	0.22-0.56	3
350-449	3.0	—	1	1.6	—	1	1.40	—	1
450-549	2.9	2.6-3.1	2	2.4	2.2-2.5	2	0.49	0.41-0.58	2
550-649	2.9	2.4-3.4	2	1.9	1.8-2.0	2	0.94	0.53-1.35	2
650-749	3.2	—	1	2.8	—	1	0.49	—	1

again no downward trend can be noted. *Calcium* concentrations are within the normal range for newborns and adults, and vary little.

Protein concentrations are quite low during this period of fetal life. In Table 3 an indication of a slow rise may be seen. Both albumin and globulin fractions are decreased as compared with term values. Nevertheless, it may be noted in Table 4 that the relative concentrations of the several globulin fractions differ somewhat from the normal mean values at term found with our technique. Attention should also be directed at the extremely high proportion of globulin observed in one fetus in the 550-649 g group. The β -globulin in this fetus was found to have

three distinct peaks. In another fetus the electrophoresis indicated a very distinct pre-albumin fraction, amounting to 3 relative per cent.

Discussion

The rise in hemoglobin concentration between the 10th and 22nd week of pregnancy has been noted previously (11, 13). This then serves as a suitable check to indicate that in general the small group of samples available for study is reasonably satisfactory.

Concentrations of sodium and potassium in the cord blood of the term infant have been reported for a large number of cases (4, 8, 10). The plasma potassium in the venous cord blood is slightly but signifi-

TABLE 4. *Globulin fractions in human fetal plasma, expressed as percentage of total protein present.*

Fetal weight in g	Globulin fraction of plasma (relative %)							
	α_1	α_2	β	γ	α_1	α_2	β	γ
	mean	range	mean	range	mean	range	mean	range
50-149	3.5	2.2-4.7	3.5	1.6-5.7	8.2	6.3-13.4	3.7	1.5-6.0
150-249	3.3	—	2.9	—	7.0	—	2.9	—
250-349	2.6	1.8-3.1	2.8	1.2-3.7	7.0	5.0-8.0	3.0	2.0-4.6
350-449	—	—	—	—	—	—	—	—
450-549	2.2	2.0-2.3	3.2	3.1-3.2	6.5	4.7-8.3	3.6	2.4-4.7
550-649	3.5	3.2-3.7	3.7	3.4-3.9	19.4	12.7-26.1	4.7	3.1-6.2
650-749	2.7	—	2.1	—	6.7	—	3.5	—

cantly higher than that of the mother. There is general agreement that the potassium concentration of the plasma of the term infant is about 5.3 mEq/L. This is clearly much lower than the values herein reported for previable infants, ranging from 6.3 to 12.8 mEq K⁺/L with a mean of 9.0. Although maternal concentrations were not determined there is no reason to expect that they were elevated above the normal range. Others have speculated that the elevated potassium in the term infant is a reflection of relative hypoxia (10). This explanation cannot be invoked without supposing very severe hypoxia at the early stages of pregnancy, decreasing toward term, a supposition for which there is no supporting evidence (12).

Sodium concentrations are likewise much elevated over adult and term infant values, which tend to cluster around 140 mEq/L and to be equal.

Taken together the sodium and potassium concentrations in the plasma of these previable fetuses strongly suggest that the placenta can effectively work against a considerable concentration gradient at least at this stage of pregnancy, thus maintaining an elevated crystalloid osmotic pressure to compensate for a lowered colloid osmotic pressure.

As previously noted by many workers

(see Bergstrand & Czar), the concentration of fetal plasma proteins are quite low early in pregnancy. In addition albumin is relatively high and, in the globulin fraction the γ -globulin is relatively low. The triple-peaked β -globulin observed in one fetus has not been previously described.

The prealbumin fraction may very well correspond to that observed by Malmnäs by a different technique.

Bergstrand & Czar described a fraction, the so-called x-component to migrate between the albumin and the α_1 -globulin of fetal plasma. We have also observed this component on several occasions.

Summary

1. In the previable human fetus, hemoglobin concentration and hematocrit are low but tending to rise with advancing age and size. Mean corpuscular hemoglobin concentration is unaltered. Plasma proteins are much reduced and their electrophoretic pattern differs from those of newborn infants and adults.

2. Plasma-concentrations of potassium and sodium are elevated above corresponding values at term and in the adult. Calcium concentration in the plasma of these previable fetuses is the same as that at term and in the adult.

Quelques constituants du sang veineux ombilical de fœtus humains avant la naissance

Chez le fœtus humain, avant la naissance, la concentration en hémoglobine et le volume des globules sanguins sont faibles, mais tendent à augmenter au fur et à mesure que le fœtus avance en âge et se développe. La concentration moyenne de l'hémoglobine globulaire est normale. La concentration des protéines dans le

plasma est nettement inférieure à la normale et les résultats de leur analyse par électrophorèse sont différents de ceux que l'on trouve chez les nouveau-nés et les adultes. Les concentrations du potassium et du sodium dans le plasma sont supérieures à celles que l'on trouve chez les bébés nés à terme et chez les adultes. La concentration du calcium dans le plasma de ces fœtus avant la naissance est la même que chez les bébés nés à terme et chez les adultes.

Gewisse Bestandteile im venösen Nabelschnurblut bei noch nicht lebensfähigen menschlichen Föten.

Bei dem noch nicht lebensfähigen menschlichen Fetus sind die Hämoglobinkonzentration und der Hämatokrit niedrig, haben aber eine Neigung, mit fortschreitendem Alter und zunehmender Körpergrösse anzusteigen. Die mittlere Hämoglobinkonzentration in den Blutkörperchen ist unverändert. Plasmaproteine sind stark herabgesetzt und ihr elektrophoretisches Verhalten unterscheidet sich von dem des Neugeborenen und Erwachsenen. Die Konzentration von Natrium und Kalium im Plasma ist über die entsprechenden Werte beim vollreifen Neugeborenen und Erwachsenen erhöht. Die Kalziumkonzentration im Plasma dieser noch nicht lebensfähigen Föten ist dieselbe als die beim reifen Neugeborenen und Erwachsenen.

Algunos elementos de la sangre venosa umbilical de fetos humanos previables.

En el feto humano previable, la concentración de hemoglobina y el valor hematocrito son bajos pero tienden a aumentar con la edad y el tamaño. La concentración de hemoglobina corpuscular media se halla inmodificada. Las proteínas plasmáticas están muy reducidas y su patrón electroforético difiere del de los recién nacidos y adultos. Las concentraciones plasmáticas de potasio y sodio son elevadas en relación con las cifras correspondientes a los niños a término y adultos. La calcemia de estos niños previables es la misma que la de los fetos a término y adultos.

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Department of Obstetrics and Gynecology
Sabbatsbergs sjukhus
Stockholm
Sweden

CASE REPORT

Sarcoma Botryoides in Children

A Report of Two Cases

by LUDVIG OKMIAN and ALEXANDER LIVADITIS

From the Surgical Department of the Pediatric Clinic, Karolinska Sjukhuset

Sarcoma botryoides is a rare and highly malignant tumor of the vagina and uterus. The neoplasm has been variously called "carcinosarcoma", "rhabdomyosarcoma", "myxoma enchondromatodes arborescens colli uteri", "mixed mesodermal tumor", "dysontogenetic mixed tumor", and so on, depending upon the predominating type of tissue. The literature of the subject has become so confused through complicated terminology, that the necessity for more accurate classification has been repeatedly realised. Recently Sternberg *et al.* (14) considering these tumors as embryonal derivatives of the Müllerian apparatus, proposed the term "mixed malignant Müllerian tumor".

The first description of sarcoma botryoides as a primary tumor of the vagina was made by Guersant (8) in 1854. Since this early report no less than 150 cases have appeared in the literature. The tumor has been encountered in postmenopausal women as well as in intrauterine life, but the majority of the reported cases have been observed in infancy (1, 2, 3, 10). The predominating site and age incidence of the neoplasm are shown in Table 1 (McFarland 1935).

TABLE 1. Age incidence according to site of origin of sarcoma botryoides J. McFarland (10).

Age (yr)	Vaginal (no. cases)	Uterine (no. cases)	Totals
Under 2	42	5	47
2-22	74	22	96
Over 22	0	39	39

During the last 6 years two children with sarcoma botryoides vaginae were admitted and operated upon in the Surgical Department of the Pediatric Clinic, Karolinska Sjukhuset.

Case Reports

Case 1. Febr. 1957, an otherwise healthy child aged 2 years, was admitted to a provincial hospital because her mother had noticed a tumor protruding from the vulva. There had been no bleeding or discharge. On admission to our Clinic (20.2.-57) a large polypoid mass was found extruding from the vagina. The growth was attached to the anterior and right vaginal wall with extension into the right fornix. Palpation of the abdomen was suggestive of a fixed tumor in the hypogastrium extending upwards to the umbilical level. A portion of the protruding tumor was excised for histological examination. The report suggested malignancy.

nancy, but failed to identify the histological patterns of the growth. After consultation with the radiotherapists, irradiation was rejected as ineffective and surgery considered. On March 14, 1957, total hysterocolpectomy by the combined abdominoperineal approach, was performed. There was no gross evidence of any malignant extension within the peritoneal cavity. The tumor mass was found to be firmly adherent to the bladder neck and urethra, with apparent infiltration into the bladder base. The urethra was removed with the tumor and a permanent cystostomy instituted. The abdomen was appropriately closed while the perineal wound was packed to control bleeding.

Pathologo-anatomical examination revealed a 9 cm polypoid tumor mass of soft consistency, filling the distended vagina. Sections through the tumor mass showed densely cellular sarcomatous tissue with occasional foci of myxomatous appearance. Additional sections from the vagina showed normal squamous epithelium. There was no evidence of malignant involvement of the uterus whatsoever. The neoplastic growth was composed mainly of elongated cells with irregular nuclei and linear cytoplasmic processes. The histological features of the tumor were identical to those encountered in the so called "sarcoma botryoides".

After the operative procedure, the patient developed signs of bladder obstruction and ascending urinary infection. Her general condition progressively declined and she died at home, 3 months after operation. No information was available about terminal symptoms. No autopsy was carried out. The interval between onset of symptoms and diagnosis of the disease was 10 days.

Case 2. In April 1957 a 4½-year-old child was admitted to our Clinic with a history of small vaginal bleedings of 4 days duration. On examination a cluster of gelatinous polyps growing from the upper vagina was found. The polypoid mass bled very easily. Per rectum the growth was found as an egg-sized, movable tumor, without apparent extension to neighbouring tissues. Two of the

polypi were avulsed and sent for histological examination. The pathologist's report was sarcoma botryoides.

On May 2, 1957, total hysterocolpectomy by the combined abdominoperineal approach was performed. There were no signs of metastatic growths within the peritoneal cavity. The neoplasm appeared to involve the vaginal walls without infiltrative extension to the neighbouring tissues. Examination of the surgical specimen revealed an orange-sized soft, gray polypoid bulbous mass of high vaginal location. The microscopic findings were comparable with those described in the previous case report.

The postoperative course was complicated by urinary retention. One month after operation, transurethral resection of the bladder neck was performed but the amount of residual urine kept increasing. The patient was readmitted on July 15, because of further bleedings. Examination showed recurrence of the polypoid growth similar to the neoplasm previously described. The patient's last admission was on November 13 because of urinary and intestinal obstruction. X-ray examination showed no evidence of metastasis in lungs or vertebrae. Rapid deterioration of her general condition and uremia resulted in death 9 months following surgery.

The interval between onset of symptoms and diagnosis of the disease was 1 week.

Autopsy: Inspection of the pelvic area revealed a soft, friable tumor mass completely filling the pelvis and protruding through the vulva (weight 875 g). The kidneys and ureters were markedly distended. Both ureteral orifices in the bladder were blocked by a neoplastic mass. The intestine and colon were greatly dilated showing serosal tumor involvement. The retroperitoneal lymph nodes showed large metastatic lesions. No metastasis in the liver, kidneys, lungs, brain or skeleton were demonstrated.

Pathology

The prevalent gross characteristic of sarcoma botryoides is the presence of a

polypoid, grape-like mass, of cervical or vaginal location. The growth appears as fleshlike, pinkish friable polyps, which are edematous and show superficial foci of necrosis and hemorrhage. On cross section cystic cavities intermingled with areas of necrosis and suppuration are found. Microscopically the neoplasm is composed of round or spindle cells bound together by a loose, myxomatous appearing stroma.

Distinction has been drawn between those tumors composed only of connective-tissue elements and those containing multiple heterologous components such as bone, cartilage, striated muscle or epithelial glands. The latter show a definite histologic similarity to Wilms' tumor of the kidney where neoplastic mesenchymal elements and epithelium appear intermingled without sharp distinction (14).

The usual spread of the tumor is by direct invasion of adjacent pelvic organs, particularly the bladder. Dissemination through the lymphatics and blood stream, though rare, has been reported (4, 5, 14, 17).

At the time of operation, no metastatic extensions within the abdominal cavity were demonstrated in any of our patients.

Symptoms

Vaginal bleeding and a polypoid mass lying in or protruding from the vagina are the initial manifestations. Purulent discharge as a result of tumor necrosis and infection may be present. As the neoplasm progresses in size, it distends the vagina and produces vesical irritability and rectal tenesmus. The clinical behaviour of the tumor proves it to be highly malignant with a marked tendency for frequent re-

currences and rapid local progression. Invasion of the bladder or rectum may result in fistula formation and local or generalized infection. Death is usually due to hydronephrosis and uremia from vesical or ureteral occlusion. Both of our patients suffered postoperatively from urinary obstruction while one of them is known to have died in uremia.

Diagnosis

In cases of sarcoma botryoides, early diagnosis and immediate surgery, constitute the only hope of cure. Incorrect diagnosis or extensive trial on preliminary irradiation are still greatly responsible for undue delay. In this respect attention has been drawn by Duncan and Fahmy (3) to the extreme rarity of benign cervico-vaginal polyps in childhood. These authors suggested that any polypi protruding from the vulva in a child, should be diagnosed provisionally as sarcoma botryoides. Clinical diagnosis must be confirmed by biopsy. This examination, however, should not be regarded upon as absolutely reliable, as there are recorded in the literature cases of sarcoma botryoides, where initial pathologic reports excluded malignancy (1, 9). This is attributable to the fact that the malignant nature of the growth may be masked by benign squamous epithelial covering and myxomatous stroma (3).

Treatment

Regardless of the treatment employed, this tumor almost uniformly progresses to a fatal termination. Various combinations of local excision, irradiation, and nitrogen mustard treatment, have been of no benefit. For the present, extensive surgery

holds the only hope of cure. The results in the individual cases of Meigs (16), Shackman (12), Richmond (11), and Gross (7) seem to justify this conception. But how extensive must this surgery be? Sternberg *et al.* (14) believe that "Since pelvic and inguinal lymph-node metastases occur, minimal surgical therapy should include total abdominal hysterectomy, with wide excision of the vaginal cuff, bilateral salpingoophorectomy, and a thorough pelvic and inguinal lymph-node dissection." Swenson (15) recommends total pelvic exenteration since preservation of the anal canal has been unsuccessful in his experience. Massive resection of all pelvic organs including the rectum and anus have not been reported. This procedure is a major one having moreover the disadvantage of leaving the patient with a permanent colostomy and ureterocutaneous ileostomy.

Summary

1. Two new cases of sarcoma botryoides vaginae have been reported.

2. "Sarcoma botryoides" is an unsatisfactory descriptive designation for a rare and highly malignant tumor of the vagina or uterus.

3. The occurrence of the growth is higher in the younger age groups, where vaginal location predominates.

4. Spread is usually effected by direct extension to contiguous viscera. Distant metastases, though rare, have been reported.

5. Local excision, irradiation and chemotherapy have been of no value. Radical resection of all pelvic organs, with diversion of the urinary and intestinal tracts should be considered.

Deux cas de sarcome botryoïde chez des enfants

Description de deux nouveaux cas de sarcome botryoïde du vagin. Le terme de « sarcome botryoïde » est une dénomination descriptive peu satisfaisante qui désigne un type rare et extrêmement malin du vagin ou de l'utérus. Cette tumeur se rencontre plus fréquemment dans les jeunes catégories d'âge où la localisation vaginale prédomine. Sa diffusion s'effectue habituellement par extension directe aux viscères adjacents. Les métastases éloignées sont rares, mais on en a cependant signalé. L'excision locale, la radiothérapie et la chimiothérapie n'ont donné aucun résultat. La résection radicale de tous les organes pelviens avec dérivation des tractus urinaire et intestinal doit être envisagée.

Sarcoma botryoides bei Kindern. Bericht über zwei Fälle.

Zwei neue Fälle von Sarcoma botryoides der Scheide werden mitgeteilt. "Sarcoma botryoides" ist eine unbefriedigende beschreibende Bezeichnung für einen seltenen und sehr bösartigen Tumor der Scheide und Gebärmutter. Das Vorkommen der Geschwulst ist grösser bei jüngeren Altersgruppen, bei denen die Lokali-

sierung in der Scheide überwiegt. Das Fortschreiten erfolgt gewöhnlich durch direktes Übergreifen auf benachbarte Eingeweide. Fernmetastasen sind, wenn auch selten, gemeldet worden. Örtliche Entfernung, Bestrahlung und Chemotherapie haben sich als wertlos erwiesen. Radikale Resektion aller Beckeneingeweide mit Ablenkung des Harn- und Darmtraktes müsste in Betracht gezogen werden.

Sarcoma bothroides en los niños. Presentación de dos casos

Se presentan dos nuevos casos de sarcoma bothroides de la vagina. El término de « sarcoma bothroides » es una denominación descriptiva poco satisfactoria para un tumor raro y muy maligno de la vagina o del útero. La frecuencia del tumor es mayor en los jóvenes en que predomina la localización vaginal. La difusión se efectúa por lo general por extensión directa a las vísceras contiguas. Se han publicado metástasis a distancia, aunque raras. La excisión local, la irradiación y la quimioterapia carecen sin utilidad. La resección radical de todos los órganos pélvicos, con derivación de las vías urinarias e intestinal merece ser considerada.

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Surgical Department
Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
Sweden

SUMMARIES OF SUPPLEMENTS

Breast Feeding and Artificial Feeding. The Norrbotten Study

by OLOF MELLANDER, BO VAHLQUIST, TORE MELLBIN
and COLLABORATORS

(Supplement 116)

This monograph opens with a survey of the literature comprising 20 pages. In a separate section on the comparative biochemistry of human and cow's milk the usual chemical data are discussed and in addition the results given of certain recent studies.

The series consists of 402 infants. In those cases in which breast feeding could not be carried through to the full the diet was supplemented with a 1:1 mixture of cow's milk and water with 5% of sugar and 1% of wheat flour. Every child was frequently and regularly examined during the first year of life, and subsequently kept under observation in accordance with the standard child-welfare-centre pattern. Special investigations involving clinical examination, blood tests for chemical and serological estimations, and at certain ages X-ray of the bones and dental examination were carried out at birth, "7½ months" (90% of the children were aged 6-9 months), and "30 months" (90% aged 26-34 months). The time table for the special investigations and for certain of the immunization-procedures is shown in a figure.

Results. The series was divided into 4 groups, according to the duration of breast feeding. The confidence interval was systematically calculated between the infants weaned very early (Group I) and very late (Group IV) from the breast. The findings for the intermediate groups were also taken into account in the statistical assessment of the results, but only in part of the series were they utilized in estimating confidence intervals.

A survey of those results that led to the calculation of confidence intervals is to be found in a table and are fully commented upon.

With regard to *physical development* (weight, height, ossification centres), the values were significantly higher at "7½ months" for Group I (early weaned) than for Group IV (late weaned).

The frequency of certain *acute infections* (cough, otitis media) was higher in Groups I and II (early weaned) than in Group IV (late weaned), but the differences are moderate, and the degree of significance does not exceed the 5% level. A comparison with regard to different types of infection

shows a higher incidence in Group I (early weaned) than in Group IV (late weaned).

The incidence of caries at "30 months" is higher in Group II (early weaned) than in Group IV (late weaned), but the degree of significance does not exceed the 5% level.

The antibody response to diphtheria and pertussis immunization shows no significant difference between any groups; and no significant difference is found with respect to influenza vaccination, but in this case there was very little material.

Concerning the serum biochemistry, there are notable differences at "7½ months"

with regard to gamma-globulin, calcium, phosphorus, and alkaline phosphatase.

As an appendix a comparison is made between two sub-groups of Group I, of which one had received a 1:1 feed prepared with fresh milk and the other a similar mixture made from a dried-milk preparation. A significant difference was revealed with respect to weight-gain and the serum level of alkaline phosphatase.

It is stressed that the results presented refer to a certain defined type of artificial feeding, and furthermore that all the participating infants were kept under strict clinical observation.

Errata

p. 31, Table 1 should read as follows,

	Human milk
Total protein	1.0 - 1.5
— — —	
Total whey protein	0.5 - 1.0

p. 34, Table 5 should read as follows,

	Human milk	Cow's milk
Proteins	g 1.0 - 1.5	
— — —		
Choline	mg 9	13

In Honour of Bo Vahlquist on His Fiftieth Birthday

April 11th 1959

Edited by S. SJÖLIN

(Supplement 117)

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The Proceedings of the Twelfth Northern Pediatric Congress
Helsinki, Finland, June 29—July 2 1958

Edited by NIILLO HALLMAN
Secretary General

(Supplement 118)

This supplement contains the opening address of the President C.-E. Räihä, the minutes of the proceedings with summaries of the 38 papers and of the discussions and short reports of the 56 scientific exhibitions. The main topics discussed were:

Perinatal Mortality and its Prophylaxis,
The Etiological Background of Disturbances in Micturition and The Somatic Development of the Child and Factors Influencing It.

PROCEEDINGS OF PEDRIATRIC SOCIETIES

Danish Paediatric Society

Meeting Febr 11., 1959

Erik Ryssing: Acute Poisoning with Theophyllamine in an Asthmatic Child

A case of acute poisoning with theophyllamine in an asthmatic child is reported. Following administration of 850 mg theophyllamine distributed over a period of 33 hours to a child weighing 9100 g acute symptoms consisting of pallor, tachycardia, loss of consciousness, muscular spasms, impaired respiration, cyanosis and seizures developed. The symptoms disappeared gradually over 6-7 hours. The episode was interpreted as acute poisoning with theophyllamine. The following doses of theophyllamine are recommended: 7 mg/kg rectally, 3.5 mg/kg intramuscularly or intravenously and 5 mg/kg orally. These doses should only be administered twice or at the most thrice per 24 hours. It is suggested that ready-made suppositories of 100 mg theophyllamine should be manufactured.

DISCUSSION: *Jakob Øster:* Many physicians are unaware how dangerous the dosage of theophyllamine prescribed can be. Dr Øster had seen a school child for whom Novatrophedrin tablets had been prescribed on account of cough and coryza. The child received 300-400 mg theophyllamine daily in this way until moderate poisoning developed.

Erik Ryssing & Knud Riewerts Eriksen: A Case of Pulmonary Moniliasis

An asthmatic child aged 2 $\frac{3}{4}$ years was admitted to the Paediatric Department,

Blegdams Hospital, Copenhagen, with high fever and lacunar tonsillitis, slight aphthous stomatitis and acute bronchitis possibly due to a virus infection. Following treatment with Calcipen (Leo) for two days and aureomycin for two days numerous *Candida albicans* were demonstrated in throat swabs and in the faeces. On account of increasing respiratory embarrassment of bronchostenotic type, marked cerebral anoxia and shock developed and were treated with oxygen, tracheotomy, transfusions and steroids. Numerous *Candida albicans* were demonstrated in the bronchial secretion and the diagnosis of broncho-pulmonary moniliasis established. The patient was treated with antimycotic antibiotics (Mycostatin (Squibb) and Fungizone) with good effect. The significance of broad-spectrum antibiotics in the development of secondary fungus diseases is mentioned and investigation for fungi is recommended in obscure cases. A number of communications have recently appeared in the literature concerning generalized moniliasis and, as effective antimycotics are now available, early diagnosis is of great significance.

DISCUSSION: *Jorgen Vesterdal* mentioned three cases of moniliasis which had been admitted to the Department of Paediatrics, the University Hospital, since 1952: 1) Girl, aged six years, with formation of pseudomembranes particularly in the mouth, throat and larynx and marked loss of weight. This case was demonstrated to the Society in 1957. 2) Newly born infant, birth weight 2250 g who had been healthy for six days

suddenly took ill with cyanosis, weakness and crepitations in the lungs. At autopsy moniliasis spreading from the oesophagus was found. 3) Male infant who took ill at the age of $2\frac{1}{2}$ months with extensive coating of the mouth and throat and pyrexia. The child was admitted to hospital a month later with massive loss of weight and with a peculiar thickening of the skin. An exanthema was seen periodically which resembled that seen in Letterer-Siwe's disease together with enlargement of the liver and gradually increasing muscular tone in the extremities. Biopsy of a lymph gland, similarly, suggested Letterer-Siwe's disease. The bone-marrow showed reticulosis and reduced erythropoiesis. The child was treated with Mycostatin (Squibb) and, thereafter, Delcortin (Leo) but became gradually worse and died. At autopsy no systemic disease could be found but moniliasis particularly in the oesophagus and pronounced interstitial pneumonia which did not resemble plasma-cell pneumonia. — *K. Wilken-Jensen* enquired whether skin-testing had been undertaken. He had seen an adult patient with repeated attacks of bronchitis who reacted positively to skin-testing with monilia. This patient was desensitized with good results. — *C. Friderichsen* remembered the violent cases of thrush which used to be seen. This spread to the lungs and such children died. — *E. Thamdrup* mentioned the case of a newly-born infant with a birth weight of 2200 g who was admitted to the Children's Hospital Fuglebakken, Copenhagen, on account of impaired respiration and weakness. On the fifth day of life, monilia was cultured from the bone-marrow. The infant was moribund on the seventh day but reacted well to intravenous fluid, Actocortin and Acton but was still very ill and with the thorax in the inspiratory position. X-ray of the thorax revealed marked perihilar markings. On the twelfth day, monilia could no longer be cultured from the bone-marrow but the infant was, nevertheless, treated with Fungizone intramuscularly which produced quite a marked local reaction. Since then gradual improvement has occurred. — *E. Ryssing*: Skin-tests were not

undertaken as, according to the literature, these are positive in 40–50 per cent of all adults and similarly positive agglutination tests are encountered in approximately 40 per cent even in the absence of clinical symptoms. Moniliasis most frequently begins as an oesophagitis. — *K. Riewerts Eriksen* did not consider that it was necessary, as a rule, to continue treatment with antimycotics for as long periods as the manufacturers recommend. The treatment may probably be concluded a couple of days after the cessation of symptoms.

Knud Wilken-Jensen: Purpura and Allergy to Food-Stuffs

In the Paediatric Department and the Policlinic for Allergic Children, the University Hospital, Copenhagen, 12 children suffering from purpura were examined during the years 1950–53. Of these, six had thrombocytopenia. In 11 cases, infection appeared to have been the cause and in two cases only penicillin might have been the etiological factor. During the years 1954–57 19 cases were examined of which five were due to sensitivity to food-stuffs and four were possibly due to this cause. Seven cases were due to infection and in three cases the etiology was unknown. Out of these nineteen patients six had thrombocytopenia. The five patients with purpura on account of allergy to food-stuffs were sensitive to 1) milk, wheat, barley, fish, tomatoes, 2) tomatoes, 3) milk, beef, 4) milk and, later, nearly everything else, 5) milk, fish and pork. In the first case the sensitivity disappeared after seven months while in the remaining four patients still, several years later, symptoms develop when they receive the food-stuff concerned. The diagnosis was established by skin tests and followed-up by elimination and provocation diets as cutaneous tests, as with the various blood tests, are of little use diagnostic criteria while meticulous history taking and clinical exposure reveal the etiology with certainty. Purpura on account of allergy to food-stuffs is probably more common than the literature suggests. Investiga-

tion for allergy is probably undertaken too rarely.

DISCUSSION: *Jørgen Kringelbach* had seen two cases of purpura on account of allergy to food-stuffs. One child developed purpura following celery and curly kale and the other probably following the use of cloves used as a seasoning in mince. — *K. Wilken-Jensen*: The changes in the thrombocyte

count are very irregular. Intracutaneous tests have given typical haemorrhagic reactions in some cases and occasionally with deterioration in the general condition. Provocation tests produce reactions in the course of a short time, occasionally on the following day. By and large, the symptoms are released, in particular, at periods when the patient is subject to mental stress, is tired or has sustained an infection.

Meeting March 11, 1959

Hans-Walther Larsen: Prophylaxis of Anaemia by Intramuscular Administration of Iron to Premature Infants

Out of 131 premature infants treated with supplementary iron orally (250 mg daily), 70 were treated, in addition, with Imferon (ASA) intramuscularly (75 mg). No complications were observed in connection with the treatment. On control examination at the ages of 3, 6 and 9 months, slight anaemia was found in both groups but no significant difference between the haemoglobin percentages in the two groups. It appears that intramuscular Imferon treatment can replace prophylactic iron therapy in suitable cases.

DISCUSSION: *J. F. Christensen* enquired whether the prophylactic iron therapy in premature infants could be replaced by injections of iron at e.g. three, six and nine months of age. — *P. W. Brastrup*: According to calculations it should be possible to cover the premature infant's iron deficiency by injectable iron but the experiment carried out gave, by and large, negative results. Perhaps a new series should be investigated and arranged as suggested.

P. W. Brastrup: Pigmentation of the Skin Following Injection of Imferon

Coloured slides were demonstrated to show extensive pigmentation in the gluteal region in a girl aged five years following injections of Imferon. The injections were

administered elsewhere and it had not proved possible to elucidate what precautions were taken.

Jørgen Kringelbach: Generalized Glycogenosis

A typical case of generalized glycogenosis in a boy aged $3\frac{1}{2}$ months was reported. The child was the second child of related parents. The infant was healthy and thrived until the age of six weeks. Thereafter, dyspepsia occurred with increasing weakness and gradually also cardiac symptoms. Investigation revealed a globular enlarged heart, typical ECG, marked macroglossia, hypotonia of the muscles and at the same time pseudohypertrophy. Biopsy from a muscle confirmed the diagnosis. The laboratory findings were normal apart from considerably raised serum transaminase and moderately raised serum potassium and simultaneously slightly lowered sodium and chloride values. The infant died a month later from cardiac and respiratory failure. The autopsy findings were characteristic. The case appears to be the first published from Scandinavia.

DISCUSSION: *A. Soeborg Ohlsen* demonstrated the findings at autopsy. The muscle fibrils proved, on ordinary staining, to be replaced by cavities which special staining proved to be accumulations of glycogen. To a question from *C. Friderichsen*, *J. Kringelbach* replied that glycogen in this disease,

as in von Gierke's disease, is normal glycogen. The disease is probably due to an enzymatic defect.

Henrik Wulff: Generalized Mycosis in a Boy Aged 4 Years

A boy aged four years was admitted following slight generalized symptoms for two months for which he had been treated with penicillin both as injections and orally. On admission to the Paediatric Department, the Copenhagen County Hospital in Gentofte, the boy had severe bilateral pneumonia and was so ill that treatment with steroids was necessary. During the following months he developed numerous relapses which were first dominated by pulmonary symptoms and later after 4½ months hospitalization by pronounced cerebral affection. After five months this produced acute symptoms on account of increased intracranial pressure. Craniotomy showed diffuse macroscopic and microscopic changes both in the grey and the white matter. Two months after operation treatment with Mycostatin was instituted and continued throughout six months during which the objective pulmonary changes disappeared entirely and spotty calcification developed in the brain. The case was probably due to generalized moniliasis. Despite numerous animal inoculations from various tissues, including the brain, it did not prove possible to demonstrate the fungus. The serological reactions were negative. A series of microscopical examinations from tissues all revealed uncharacteristic inflammatory changes and necrosis. The diagnosis is, therefore, based upon the favourable response to treatment with Mycostatin. All other forms of antibiotics and chemotherapy were without result. All signs of acute infection had disappeared a year after the commencement of the disease but left-sided hemi-paresis, symptomatic epilepsy, retarded speech development and considerable mental and intellectual retardation remain.

DISCUSSION: *Chr. Hansted:* Steroid therapy probably had a direct lifesaving effect in this case although the exact mechanism is not

entirely elucidated. — *Johs. Melchior* was of the opinion that fungus infection of the brain is not as rare as usually presumed. He had observed a series of oligophrenic children in U.S.A. in whom fungus infections of the brain were demonstrated at autopsy.

Chr. Hansted: Excessive Acidosis with Pre-renal Anuria, Paralytic Ileus and Respiratory Paralysis following Administration of Salt with the Food

A case of salt-poisoning is reported in a female infant aged three months which developed following the administration of 50–75 g of a milk mixture in which salt had been substituted for sugar (4–6 g NaCl). The infant was brought to hospital in coma and with hyperpnoea, violent motor restlessness and seizures on account of cerebral irritation and compensatory hypocalcaemia. On admission, the serum sodium was 194, chloride 170 and bicarbonate 10 mEq. The pH of the blood was 6.94 and fell to 6.80 and the $p\text{CO}_2$ was 62 increasing to 110 mm Hg. During the course of the first two days the triad of symptoms given in the title developed and the patient had to be ventilated artificially for three weeks. It was observed that the efficacy of the ventilation was of decisive significance for the development of renal and intestinal symptoms as the oliguria and intestinal paresis relapsed on several occasions when the patient became hypoxic. The coma did not disappear until after two weeks and the child suffered from symptoms of cerebral seizures for six months (sequelae of secondary metabolic and anoxic injuries?) but has now been free from symptoms for six months and has developed normally. No renal lesion has been demonstrated.

DISCUSSION: *P. W. Braestrup:* Perhaps exchange transfusion should have been performed at an early stage to brake the cycle: anuria-hyperpnoea. — *Chr. Hansted* considered that, in such cases, oxygen should be administered first and, thereafter, glucose solution or dilute saline solution intravenously with meticulous control on account of

the danger of overdosage of fluid. Exchange transfusion could probably remove approximately 25 per cent of the retained salt but could be repeated.

Vagn Christensen: Chronic Myeloid Leukaemia in a Four-Year-Old Boy

A boy aged 4 $\frac{1}{2}$ years had suffered from increasing fatigue, dyspnoea on exertion, anaemia and enlargement of the spleen for a year. The bone-marrow revealed chronic myeloid leukaemia. Remission was obtained with 2 $\frac{1}{2}$ mg purinethol per kg body weight and this was maintained with 1 mg per kg for about six months. Thereafter, myeloblastic crises and death occurred despite

treatment with Methotrexate and Meticorten. No symptoms were apparent in the skin nor in the skeletal or nervous systems and no particular infections had occurred in the course of the disease.

DISCUSSION: *J. Kringelbach* reported a similar case in which radiation therapy resulted in good remission. — *J. Flamand Christensen* had treated a child with chronic myeloid leukaemia first with cortisone apparently without effect and later with radiation after which good remission occurred. — *Vagn Christensen* had the impression that the condition had deteriorated in the patient mentioned during treatment with Meticorten.

Meeting April 8, 1959

Johannes C. Melchior: Impressions from U.S.A.

A brief account was given of the work in the neuropathological laboratory in the oldest institute for mental defectives in U.S.A., The Walter E. Fernald State School in Waverley, Boston, under the charge of Dr *Clemens E. Benda*. Mention was made of the special conditions and the tasks: classification of the post-mortem material from ten years, investigation of idiopathic, intracranial, familial calcification and the possible connection between this condition and diffuse sclerosis, chronic and subchronic mycotic infections as the cause of acquired mental deficiency. Finally, the paediatric departments in Boston were mentioned and the conditions of education, participation in meetings and post-graduate courses.

Olaf Steinicke: Schönlein-Henoch's Purpura with Serious Complications

Two cases of Schönlein-Henoch's purpura were mentioned: 1) A boy aged 10 years with haemorrhages into the skin, intestine and kidneys together with joint episodes and varying oedema. The clinical picture

was gradually dominated by nephritis with transition to nephrosis. The child was discharged after 11 months in hospital with slight proteinuria and haematuria. 2) Girl aged over 7 years who first showed joint symptoms, severe intestinal haemorrhages, slight skin haemorrhages and pronounced hypertension together with seizures and transient pareses. Later serious renal complications developed with violent proteinuria and tendency to oedema. Simultaneously, the hypertension continued and the child died after 34 days in hospital. A clinical picture such as the latter case occurs extremely rarely and the hypertensive and neurological changes are considered to be produced by vascular changes in the cerebrum. The therapy in Schönlein-Henoch's purpura is mentioned. Steroid therapy was tried in both cases but without effect. The question is raised whether treatment with rigid diet should not be attempted in as serious a case as the latter as allergy to food-stuffs as the etiological precipitating factor cannot be excluded.

DISCUSSION: *H. Dyggve*: In the Paediatric Department, the University Hospital, Copenhagen, 14 cases of Schönlein-Henoch's

purpura were seen during the past ten years. Out of these, nine had joint symptoms, ten oedema, eleven abdominal colic, three macroscopic and seven occult melaena, three were submitted to laparotomy on account of abdominal pain and in one appendicitis was found, two had terminal ileitis, two hypertension and one seizures. In only two patients were the skin reactions positive and elimination diet did not render convincing results. None of these patients died. — *Oluf Andersen*: In Queen Louise's Hospital for Children 12 cases of Schönlein-Henoch's purpura have been seen in the past 10 years. Out of these, 10 patients had had preceding infections of the throat. Two patients, in particular, were mentioned: 1) This patient had been admitted two years previously elsewhere with Schönlein-Henoch's purpura and was now admitted with slight albuminuria and hypoproteinaemia. Following tonsillectomy complete recovery took place. 2) A patient was admitted with purpura but developed a clinical picture which resembled rheumatic fever with cardiac complications, murmurs and enlargement of the heart. A possible focus of infection must be sought after even although the AST is normal. In several of the cases mentioned the purpura disappeared following treatment with Ascorbin while cortisone appeared to be without effect. — *Chr. Hansted*: During the past 12 years, 24 patients with Schönlein-Henoch's purpura were admitted to the Paediatric Department, the Copenhagen County Hospital in Gentofte, and of these 19 were admitted during the past five years. Ten of the patients had macroscopic or occult intestinal haemorrhage. Four patients presented special symptoms: Two suffered from invagination, one showed symptoms of nephritis for three months and another was transferred to a surgical department where laparotomy was undertaken on account of abdominal pain and massive subserous haemorrhage was found. Later, massive proteinuria and haematuria developed and still persist nine months later. The majority of the cases mentioned developed on infectious-allergic basis and in one case there was possibly

allergy to food-stuffs. — *E. Ryssing*: A boy aged 11 years had experienced recurrent abdominal pain for 4-5 years and had been admitted to hospital on four occasions on three of which no definite diagnosis could be established. When admitted to hospital on the last occasion, the boy had headache, nausea and slight pyrexia. Two days later he developed purpura and occult intestinal haemorrhage and liver damage could be demonstrated together with low prothrombine value, raised serum transaminase and urobilinuria. — *K. Wilken-Jensen*: A number of the patients in whom the disease is interpreted as allergy to food-stuffs have probably an allergy to food-stuffs which is precipitated by infection. In these cases, skin tests are of only limited value but nearly all allergies to food-stuffs will disappear in the course of some years.

Discussion of the Experience to Date with DPT (Diphtheria-Pertussis-Tetanus)-Vaccine. *H. Kreutzfeldt*: Information concerning approximately 300 children vaccinated with DPT-vaccine is now available, a total of more than 1000 vaccinations. Complications were encountered in 6.5 per cent of the vaccinations and the most serious of these were a couple of cases with abscess development, probably nosocomial. During the period of vaccination 30 of the children had been exposed to infection with whooping cough and two developed the disease. Both of these were vaccinated for the first time simultaneously with exposure to the disease. Dr Kreutzfeldt was of the opinion that the experiment should be continued and thereafter discussed with The National Serum Institute which is interested in information about possible complications after first, second, third and fourth vaccinations. — *A. Biering*: It is doubtful whether the information obtained concerning the incidence of complications is entirely reliable. Dr Biering considered that such information depended upon the interest taken by the leaders of the nurseries. — *P. Plum*: It is recorded in the literature that pertussis vaccination implies greater risks than other vaccinations.

Many parents state that fits occurring in children first commenced following vaccination for whooping cough. — *H. Kreutzfeldt* and *P. W. Bræstrup*: The question whether

DPT vaccination should be employed more widely must further be discussed with the National Serum Institute.

Meeting May 20, 1959

Rich. Ege: Principles in the Rational Evaluation of Food-Stuffs and Diet in Respect of Nutrition

The value of food-stuffs must be estimated according to the content of vital nutritional substances in relation to the requirement of the human organism of such substances. The optimal requirement of the individual vital nutritional substances is not known with certainty but norms have been established which are suitable as a measurement of the diet and the food-stuffs. If the diet is composed so that it contains the recommended quantities of the 8-10 necessary nutritional substances on a basis of the natural content in ordinary food-stuffs it will contain the approximately 40 known vital substances, and probably the unknown substances also in adequate quantities. For economic reasons, grain products must constitute a considerable fraction of the diet so that vegetables, milk and meat can be afforded.

Out of the grain products, oatmeal is nutritionally considerably richer than rice, maizena and unfortified whole meal flour. The total Danish consumption of the six groups of nutritional substances remains surprisingly constant. The consumption of the individual nutritional substances within the group is more variable and depends upon habits, taste and economy. Average calculations of the consumption of food-stuffs cannot be employed to evaluate the growth and welfare of an isolated individual. In an investigation of the diet in 100 households with 5-600 individuals only ± 10 per cent deviation from the average consumption of grain products was found but, in respect of oatmeal, the deviation varied from 0 to 400 per cent. The investigation suggests that increased employment of oatmeal is compensated by decreased consumption of the

other grain products. As oatmeal with its content of 1 per cent calcium phosphate belongs to the more valuable grain products, its substitution for the other products, and particularly flour products, tends to produce an increase in the dietary content of nutritional substances. Even when a large oatmeal consumption is concerned this constitutes, as a rule, only a fraction (as a rule less than $\frac{1}{3}$) of the total consumption of grain products. When the caloric consumption is low, the consumption of oatmeal was on an average found to be low and the same was the case in the families with numerous children. Why do school doctors condemn oatmeal? Is it on account of the massive abuse of sugar with which it may be associated? It should be noted, however, that no correlation was observed between the consumption of oatmeal and sugar.

P. W. Bræstrup: The Doctor's Evaluation of the Child's Diet

The correct diet should maintain the child in health, active and thriving, provide resistance to infections, keep the teeth free from caries and ensure the maximum growth. The optimal growth curve of the individual child is given. The demonstrated increase in the average height in the more recent decades is only found for the groups in whom an improvement in the state of nutrition can be demonstrated. The nutritional norms which are employed are worked out on a basis of balance experiments, animal experiments and observations of groups on uniform diets. The current standards can now be accepted generally but doubt remains whether the norm for protein (12-14 per cent of the total caloric consumption) is adequate. There is a tendency now to state the

norms in relation to the chronological age instead of the weight. Further, in evaluating the diet, the average consumption cannot be relied upon. A great number of statements are available all of which warn against too great employment of grain products. Considering the cases seen by the doctor where children have developed various abdominal symptoms following massive consumption of oatmeal it must be justified to condemn the misuse of raw oatmeal particularly as this massive misuse appears to be limited to a limited number of households. Warnings concerning bad dietary habits are justifiable in the improvement of children's diet.

J. J. Holst: The Dentist's Evaluation of the Child's Diet

The conception of the significance of diet for the incidence of caries has varied, and it has not been successfully demonstrated that the incidence of caries can be influenced solely by dietary changes but, on the other hand, the local processes in the buccal cavity are of decisive importance. The dentist should, however, participate actively in the nutritional campaign because nutrition is of significance during the prolonged development of the teeth. By means of propaganda, attempts may be made to prevent exaggerated consumption of the food-stuffs which involve local processes in the buccal cavity, among these raw oatmeal, and eating between meals and sweets should be warned against.

DISCUSSION: *Sv. Heinild:* A single factor in the diet, such as oatmeal, cannot be judged alone but the diet, as a whole, must be evaluated. He had seen children in institutions who thrived well on a diet which must be considered to be inadequate according to the current norms while obese children lost weight on the same diet. — *E. Begtrup* stated that it was he who had recommended raw oatmeal about 1920. Children like it and he has never seen any digestive disturbances on account of the consumption of raw oatmeal but, naturally, every food-stuff can lead to digestive disturbances if employed incorrectly. — *Henning Andersen:* A number

of children develop abdominal colic and constipation which disappears completely when the breakfast consisting of raw oatmeal is replaced by something else. In such cases warnings against raw oatmeal are justified. — *B. Friis-Hansen:* Half of the population of the world exist on diet in which grain products constitute up to 90 per cent of the calories and in such peoples the incidence of caries is low. — *A. Johannesen* was of the opinion that children who eat a great deal of cheese have good teeth. — *G. Kjoller:* A series of school children in Bornholm were questioned about their diet and this information was compared with the dental status but no definite connection between the two factors was found. — *F. Bundgård-Jørgensen:* We require more investigations of the teeth in children of pre-school age and comparisons with their diet, particularly concerning the consumption of sugar in sweets and carbohydrate in cakes. There can be no doubt that the dental status can be employed to evaluate the diet in respect of these two things. — *J. J. Holst:* Perfectly nourished children may also develop caries. Caries cannot, therefore, be regarded as the expression of inadequate diet. The fluoride content of the drinking water is of great significance in this connection. Dr Holst is of the opinion that dietary habits and consumption of sweets can be influenced by propaganda. — *P. W. Bræstrup:* Oatmeal as such is not a poor food-stuff but it may be misused and this must be counteracted. If the day is begun with a poor breakfast consisting of meal and carbohydrates, this cannot be corrected nutritionally in the course of the day. — *R. Ege:* Every form of misuse may be advised against but it is difficult to state where the limits for the misuse exist. Convincing investigations concerning nutrition in man are few. These must extend over long periods before the results can be recorded. Where many individuals are concerned, the Danish diet, particularly for children, does not fulfil the proposed and recommended values.

Folke Tudvad, Copenhagen

Swedish Pediatric Society

Meeting May 23, 1959

B. Hagberg, L. Olding and L. Philipson:
Two Cases of Listeria Infection in the New-born

The two cases represent the main types of listeriosis in early infancy, i.e. acute meningitis and infantiseptic granulomatosis.

Case 1. Girl, eight weeks premature with a birth weight of 1590 g. Her first two weeks of life were uneventful. She then suddenly became dull with irregular breathing, colour changes but no fever and no meningeal signs. Lumbar puncture revealed a suppurative meningitis with 9500 white cells per ml and a protein content of 640 mg per 100 ml. Microscopic findings on stained smears gave the suspicion of Listeria infection, which was later verified by isolation of Listeria monocytogenes Type 2 from the liquor specimen. No isolations of L. monocytogenes were obtained from nose and throat, faeces and urine specimens at subsequent days. She was treated with chloromycetin, penicillin, streptomycin and gamma globulin already during the first day of symptoms and seemed to recover rapidly. However, two months old she had a progressive hydrocephalus.

The mother of this girl was ill with high fever, headache and meningismus 2 weeks before delivery. One month later Listeria was sought for in vaginal and urethral secrets faeces, urine, breast milk and discharge from nose and throat but no such organisms were isolated. She had no antibodies against the 5 serotypes of L. monocytogenes by agglutination in repeated specimens during the following weeks.

Case 2. Boy born at term with a birth weight of 2330 g and a length of 46 cm. In spite of a normal delivery he was severely asphyxiated at birth and died three hours later. At autopsy the main findings were a pronounced placentitis and vasculitis of

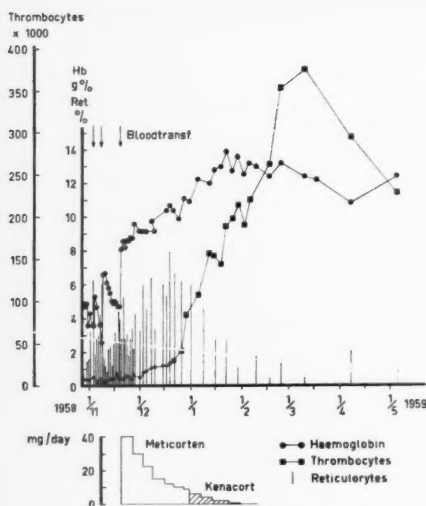
the umbilical cord, bronchopneumonia, severe ulcerations of the small intestines, slight necrotic and granulomatous changes of the liver and intracranial bleedings. Listeria monocytogenes Type 2 was isolated from blood, placenta and all organs.

The mother of this boy was quite healthy during pregnancy. Bacteriologic investigations gave no isolations of Listeria from urine, vaginal secret, nose and throat and faeces but a rise of the agglutination titres against L. monocytogenes Type 2 from $\frac{1}{10}$ five days after delivery to $\frac{1}{80}$ three weeks later was recorded. (This case will be reported in detail in Acta path. et microbiol. scand.)

DISCUSSION. *O. Brandberg:* Two newborns admitted to the Children's Clinic in the Örebro Lasarett with the clinical picture of sepsis had pyuria but no meningitis. The spinal fluid was normal.

Stig Sjölin: Myelofibrosis Treated with Meticorten®

A 6-months-old boy admitted with fever and pallor, presented a grave normochromic and normocytic anemia (Hb 4.9%), thrombocytopenia, and enlargement of the liver and spleen. The total number of leukocytes was normal, but the differential count showed 5% myeloblasts and 1% promyelocytes. Repeated bone marrow punctures gave no marrow. Histologic study of bone marrow biopsy material from the crest of the ilium revealed complete loss of normal marrow structure which was replaced by collagenous tissue with occasional promyelocytes and myelocytes and a fairly high proportion of eosinophils. No production of erythrocytes and thrombocytes could be detected. After 3 initial blood transfusions with brief effect, treatment with prednisone (Meticorten®) was attempted, which brought about a rapid and general improvement. The



Hb concentration rose, the number of thrombocytes became normalized, the liver and spleen were reduced in size. After about 2 months' treatment a complete normalization had taken place. (See Fig.) The treatment was discontinued after $2\frac{1}{2}$ months. At control 6 months later no clinical signs could be observed. The etiology of the disease could not be ascertained.

Bengt Hagberg and Lars Svennerholm: Laboratory Diagnostic Tests in Metachromatic Leucodystrophy

Three cases of late infantile metachromatic leucodystrophy, diagnosed during life, were investigated with microscopic studies of urine (according to Austin, *Neurology* 7: 415, 1957) and with chemical analyses of urine, blood and cerebrospinal fluid. Comparable studies were made on corresponding material from healthy children, and children with cerebral palsy as well as other diseases of the central nervous system. Large amounts of metachromatic granules and real metachromatic granular bodies were only found in the microscopic preparations from the three patients with leucodystrophy. A variability

of the findings from day to day was observed. Small amounts of metachromatic material in the form of free granules sometimes were also found in the preparations from healthy children, as well as from children with cerebral palsy.

Austin (*Neurology* 7: 716, 1957) concluded that a positive test for metachromatic substances in lipid extracts of urinary sediments is pathognomonic for late infantile metachromatic leucodystrophy. By partition chromatography was shown in our investigations that the metachromatic substances are sulphate esters of cerebroside (sulphatides). Contrary to Austin we found that sulphatides are excreted in all urines of normal persons investigated (infants, children, and adults). Owing to this result the sulphatides of the urinary sediment was analysed in relation to the excretion of creatinine. It was then evident that in metachromatic leucodystrophy the excretion of sulphatides was increased five- to ten-fold. A very large excretion of sulphatides was also observed in urines from healthy infants less than one year of age. Furthermore, there seem to be large variations in the daily excretion of sulphatides, why all quantitative estimations will be rough.

Sulphatides are normal constituents of serum and cerebrospinal fluid. In the three cases with metachromatic leucodystrophy analyses of sulphatides revealed normal values. In the cerebrospinal fluid of the three leucodystrophic cases the concentration of total proteins was markedly increased but the paper electrophoresis showed a normal relative distribution.

Summing up there is in late infantile metachromatic leucodystrophy an increased urinary excretion of sulphatides, which seems to parallel the microscopic findings of metachromatic bodies in toluidine blue-stained sediments. The diagnosis can be further supported by an increased content of total proteins but a normal electrophoretic pattern in the cerebrospinal fluid. A cholecystopathy with no filling of the gall bladder at cholecystography also seems to be a characteristic finding of this disease.

S. Edlund: Fibroelastosis and Congenital Heart Failure.

Åke Gyllenswärd, Owe Peterson and Claes Thorén: Surgical Results in Auricular Septum Defects — a Follow-Up Study

Thirty-seven cases of auricular septum defects were investigated before operation in the Childrens' Clinic at Uppsala. Nine cases were combined with anomalous reflux through the pulmonary veins (AVR) and 2 presented solely this defect. The majority of the operated cases were of school age. The first 18 cases were operated upon by various closing methods. Two died in connection with the operation. Since 1958 twenty operations, including a re-operation, were performed openly in hypothermia and with coronar-perfusion of arterialized blood. A one-year-old with multiple anomalies and fibroelastosis died in connection with the operation. The results were primarily very good. Cold- or anoexemia injuries did not occur. A follow-up study was routinely conducted some 7 months after the operation, with catheterization of the heart and in a certain number of cases with angiocardio-graphy. Twenty cases have been investigated up to the present. The results adjudged by the residual shunt show good improvement in half of the 14 cases operated by the closed method and in the 6 by the open method. This study proves that a postoperative observation period of about 6 months is satisfactory for appraisal of the results of surgery in ASD. Pressure increments in the right ventricle were normalized and signs of hypertrophy receded in the ECG. The relative heart volume was reduced in every case on the average of 20.6%. The electric current showed lowered right deviation on the average of 27°. A left deviation appeared in 2 cases before operation. Two cases presented protracted postoperative rhythmic disturbances. Postoperative gains in body weight in ASD children would appear of value in appraising the clinical results. Cases operated upon in hypothermia showed an average increase of 4.4 kg after 7 months against 2.6 kg for the unimproved or partly impro-

ved. Nine cases which preoperatively were considered subjectively free from discomfort, showed postoperatively a clear anamnestic improvement. In adjudging the operation risk the increased occurrence of antibiotic-resistant infections is emphasized.

DISCUSSION. *Claes Thorén:* Beside the above mentioned 20 children operated upon openly in hypothermia, 12 adults were likewise operated upon in the Uppsala Thorax Clinic without fatal issue and with clinical good results. Söndergaard himself has encountered difficulties in tightening the defects by the closed method. — *Owe Peterson:* Among the cases operated upon openly, Söndergaard's method was employed in about half of them, and thereafter we shifted to a modification suggested by Lam and thus obtained a smaller residual shunt.

G. Laurell and T. Mellbin: Bacterial Flora in the Upper Respiratory Tract in Nomadic Lapp Children

In conjunction with a broader general study of Lapp children conducted by one of us (T.M.), it appeared of interest to investigate the frequency of the commonest bacteria in the upper respiratory tract. The study comprised children attending classes 1-7 (6) in the schools for nomads in Karesuando, Lannavaara, Jukkasjärvi, Gällivare, Jokkmokk and Arjeplog. A smaller number of children were examined when they first commenced school, but the majority were usually examined after 6 weeks' attendance. The following results were obtained: *Staph. aureus* was isolated from the air passages in 69.4%. This is a high figure as compared with that reported in foreign studies of relatively isolated population groups. The frequency of staphylococci, as well as of other pathogenic bacteria, was higher in the more southerly located schools for nomads. Phage typing gave good results and about 76% of the isolated strains reacted with the phage. It was especially interesting to observe that about 25% of the typable strains reacted with Phage 71. Strains of this type are considered aetiologically connected with impetigo. *Be-*

ta haemolytic streptococci were isolated in 17.3%. The frequency varied from 2 to 36%. Type 6 proved to be the commonest and some strains belonged to Type 12. The latter is interesting because of its connection with nephritis. *Pneumococci* were isolated from 33%. Typing showed considerable scatter without preponderance of any one type. *H. influenzae* was isolated in 7.6%. No typing was done. The frequency of antibiotic-resistant strains was especially interesting in a series uninfluenced by treatment to any note-

worthy extent. *Staph. aureus* was chosen as test organism. About 92% of the strains proved sensitive to penicillin and 99% to erythromycin, streptomycin, tetracycline and chloromycetin. Slightly more than 94% proved sensitive to novobiocin.

Serological studies conducted to date have shown that for antistaphylolysin (Asta) the main titres lie under 1.4 units. More than half of the antistreptolysin titres lie over 200 units. No plausible explanation of this unexpectedly high frequency is available.

BOOK REVIEWS

Eisenstoffwechsel. Beiträge zur Forschung und Klinik. Bearbeitet von zahlreichen Fachgelehrten. Herausgegeben von Prof. Dr. W. Keiderling, Freiburg/Br.

Georg Thieme Verlag 1959. 298 sidor. D.M. 48: -

The eminent German clinician and scientist Ludwig Heilmeyer celebrated his 60th birthday on March 3rd 1959. The *Festschrift* published on that occasion is a collection of articles on a theme that for 20 years has occupied Heilmeyer, namely, the physiology and pathology of iron metabolism. His collaborator Professor Keiderling has edited the beautifully-produced book. The twenty-nine contributions from six different countries cover important aspects of the subject, and several are brilliant reviews of the research that is at present going on.

The Heilmeyer school, represented by Keiderling, Schmidt, and Wöhler, makes interesting contributions largely concerning the *tissue iron* in the form of ferritin, haemosiderin, and myoglobin, and also the changes in *iron-metabolism in infections and neoplastic disease*. Some of the articles from the United States of America are written by leaders in iron-research, and such papers as *Ferrokinetics* by Polycove from Berkely and that by Moore and Dubach from St. Louis on *Resorption, conservation, elimination, and physiological iron losses* are exemplary in their clarity. Bessis of Paris, who has made such important contributions to haematology during recent years, presents his stimulating and widely discussed electronmicroscopic observations of the position of ferritin in the synthesis of haemoglobin. The Scandinavian articles include Björkman's on *Anaemia refractoria sideroblastica*, Laurell's on *Serumproteine und Eisentransport*, Vahlquist's on *Transport iron: Circulating plasma or serum iron*, and Waldenströms on *Eisenmangel-*

krankheit. A chapter by Betke of Freiburg, *Der Eisenhaushalt des Kindes* is of particular interest to paediatricians.

Basking in the sunshine on the shores of a Swedish lake in the early summer of 1938 in the company of an old friend and colleague, and reading a fascinating little monograph recently published by Heilmeyer and Plötner entitled *Das Serumeisen und die Eisenmangelkrankheit*, I little dreamt what developments were to take place in this field during the coming 20 years, or what importance the study of iron metabolism was to attain in the interpretation of vital features of erythropoiesis and erythrocyte metabolism. It is significant that Heilmeyer, like the intuitive researcher and clinician he is, put forward in this first paper many ideas, unconfirmed at the time, which later have proved surprisingly true.

Bo Vahlquist, Uppsala

Recent Advances in Cerebral Palsy, edited by R. S. Illingworth.

J. & A. Churchill Ltd., 104 Gloucester Place, London W.1. 50 sh. net.

Professor R. S. Illingworth, in collaboration with prominent co-workers, has published this monograph on Cerebral Paresis (CP). The work has been anticipated by physicians and others engaged in CP teamwork. Introductorily Illingworth discusses the classification and frequency of CP. He adheres to the division approved by the American Academy of Cerebral Palsy, which is still being criticized, among others by English neurologists. Concerning the frequency of CP Illingworth seems to have arrived at the conclusion that it lies between 1 and 2.1 per 1000 children in England and in Scandinavia, a figure which well agrees with the latest Swedish investigation, 1.6 per

1000 children (M. d'Avignon & L. Gardeström, *Nord. Med.*, 59: 55, 1958). An excellent and well-illustrated chapter on the pathological anatomy is written by C. B. Courville. The important early diagnosis is treated by the senior author. Every possible aspect of the CP therapy is summarily touched upon. The educational problem is extensively discussed. This chapter is written by E. Schonell who stresses among other things the importance of not intermixing in one class CP-children with good intelligence and those with inferior psychic equipment, which must inevitably be the case when the number of pupils in a CP-school is too small. In other well-written chapters various authors treat of invalid gymnastics, speech therapy, occupational therapy, orthopedic therapeutic methods etc. The book, which is heartily recommended to members of CP-teams, concludes with a chapter on recent developments in brain surgery within this field.

Marcel d'Avignon, Stockholm

Edwin F. Patton: Pediatric Index. A Guide to Symptomatology, Diagnosis and Current Management.

The C. V. Mosby Co., St. Louis, 1958. Price \$13.50.

Dr. Patton's book represents a new and valuable approach toward the systematization of pediatric knowledge and practice. It is based on authoritative sources from all over the world in conjunction with the author's 35 years of personal experience. The material is very up-to-date and comprehensive in its coverage of the field. The material is arranged in item sections. Section I takes up problems confronting the doctor: complaints, symptoms, signs. These are correlated to three age-groups and their accompanying clinical features. This leads to possible diagnoses which are listed alphabetically. Section II continues with the problem of proving or disproving the probable diagnosis and suggests appropriate therapy. Section III, Special Data and Technique, contains, in alphabetical order, material

applicable to several conditions to save repetition, together with some helpful miscellaneous information. Dr. Patton's book has been in daily use for six months at the hospital and has been found an excellent guide to the practice of pediatrics. It should stand the test of time as a particularly useful aid to general practitioners, students and pediatricians.

John Lind

Edward B. Singleton: X-ray Diagnosis of the Alimentary Tract in Infants and Children.

The Year Book Publishers, Inc. Chicago, 1959. 352 pages. 215 figs. Price: 11 dollars (Sw. kronor 63.80).

The author points out in the preface that the advances in paediatrics and paediatric surgery place increasingly great demands on exact roentgen-diagnostic information, in the most widely divergent diseases of infants and children. The paediatric patient has an entirely specific group of afflictions. In this connexion, congenital anomalies are of particular importance, and require to a great extent the collaboration of the radiologist in their investigation. This applies not least to the alimentary tract. Few easily accessible surveys of acquired lesions and congenital abnormalities of this region are available. The book therefore fills a need, and the author is to be congratulated on the results. The book is easy to read, plentifully illustrated, and modern in the best sense of the term. The presentation is systematic and lucid, and is evidently based on the author's extensive personal experience.

After a review of the indications for roentgenologic examination, a description follows, organ by organ, of the technique and of the normal and pathologic roentgenologic features. Each major section is preceded by an account of the anatomic, embryologic and, to some extent, of the physiologic background of the roentgenologic findings. Mention is also made of the salient clinical features. The illustrations are, almost without exception, highly instructive, and serve as good examples of the changes described. The

references, which are taken mainly from the Anglo-Saxon literature and are brought up to date, are given in close connexion with the text, which increases the clarity. The book can be warmly recommended to all radiologists in paediatric practice, as well as to paediatricians and paediatric surgeons.

Ulf Rudhe

Wendell Johnson & Associates: The Onset of Stuttering.

Univ. of Minnesota Press, Minneapolis 1959. 276 (+ 243) pp. \$ 5.00.

Under the direction of Wendell Johnson, professor of speech pathology and psychology at the University of Iowa, a series of studies on stuttering were conducted during 1934-1957. On the basis of earlier studies bearing upon the significance of special physical facts among stuttering children respective the reciprocal relationships between children and parents, the senior author put forth the hypothesis that the essential cause of stuttering should not be sought for in the speaker, i.e. the stuttering child, but in the listener to the child's speech—generally parents—who react in a special manner to the child's speech deficiency. This book gives much detailed information regarding the employed methods and materials in a comprehensive interview procedure. The experimental group comprises parents of 246 stuttering children and the control group includes a similar number of non-stutterers. The interviews make use of some 800 questions dealing partly with the children's physical, psychological and social development, partly the parents' marital relationships, attitudes toward the child, social adjustment, as well as a separate set of questions drawn up by the Minnesota Multiphasic Personality Inventory, for the purpose of getting an evaluation of the parents' personality and psychopathological characteristics. A direct study of the children was not attempted, nor any psychologic evaluation of the parents. The material consists solely of responses to questions addressed to the parents. The further elaboration takes form

of a statistical comparison between the experimental and control groups. The results confirm the senior author's hypothesis that stuttering is caused by an interaction between a listener and a speaker, and is mainly caused by judgemental reaction of the listener, usually the mother, to the non-fluencies in the child's speech.

The interview responses fail to support the supposition that birth injuries, other brain lesions or left-handedness occur more frequently in stutterers than in other children.

It is regrettable that such a comprehensive work should not have been completed with an objective, individual study of the children and parents, inasmuch as it is dubious if the interview procedure is the proper approach for registering all the factors which may play a role in the onset of stuttering. Criticism may also be levelled against the delimitation of the experimental respective the control groups. The experimental group includes all the children who were referred to the clinic, and were considered to be stutterers by at least one parent. The analysis of the types of impaired speech suggests that certain of these children have had symptoms which usually are not diagnosed as stuttering. It is strange that the controls were intentionally chosen from a different geographical area than the experimental group. The latter lived mainly in Iowa City, and in the proximity of the clinic; the former lived more distantly from the clinic. This is motivated by the relatively large proportion of the Iowa City parents who may have known of the research project for the stutterers and thus have had more than an average degree of sophistication about stuttering. The parents who in the first place may have taken an interest in and been influenced by the clinic's research project, must have been the parents of stutterers and not parents of the control group.

The book contains such an array of details, and extreme particulars of the research project, that physicians in general will not find it interesting reading. On the other hand, the 50 pages presenting Summary & Conclusions (plus references) are highly

valuable and deserve to be published separately or in some accessible journal. Although this study falls short of giving a definitive answer to the question of the mechanism for the onset of stuttering, it contains such a multitude of valuable information that specialist clinics and investigators in this field will find much of paramount value in this book.

A.-L. Annell, Uppsala

Markus Vest: Physiologie und Pathologie des Neugeborenenicterus.

Bibl. paediat. (Basel), Fasc. 69, S. Karger, Basel/New York, 1959. Price SFr. 20: 80.

It has been claimed that the incidence of icterus of the new-born is increasing. The truth of this assertion would appear doubtful. As early as 1913, Ylppö showed that 82% of all infants had jaundice during the neonatal period. The impression of an increase in incidence is probably explained by the growing attention that has been paid to the matter since hyperbilirubinaemia of the new-born was shown to be a considerable clinical problem and not an innocent, "physiological" phenomenon.

The work under review, which was carried out at Hottinger's clinic in Basel, is concerned with the important question of the factors responsible for the "physiological" icterus of the new-born. The problem is largely assessed on the basis of personally conducted, extensive, and, in general, thorough studies on new-born premature and full-term infants. Vest concludes that the hyperbilirubinaemia in these children is due to the inability of the liver to couple bilirubin to glucuronic acid; and this is conditional for the excretion of bilirubin. Evidence in favour of this contention is provided by investigations showing an inverse relationship between the maximum serum bilirubin concentration and the total amount of bilirubin excreted in the faeces,

and especially by experiments on the excretion of acetanilide orally administered. Acetanilide is chiefly excreted in the urine as N-acetyl-p-aminophenolglucuronide, and the attachment of acetanilide to glucuronic acid also takes place in the liver. During the first days of life the excretion of this glucuronide is very low. It subsequently increases as the serum bilirubin falls, and usually reaches normal after 30-40-50 days. To judge from the blood glucuronic acid level, there is evidently no deficiency of this substance; and there is no reason to suspect that reduced secretory capacity of the renal tubules is responsible for the scanty excretion. Reduced excretion of bromsulphthalein and the inability of the liver to couple benzoic acid to glycine indicate other simultaneous defects in the liver function. Signs of immature liver function are commoner and more pronounced among premature infants than among those born at term.

Vest also considers the extent to which red-cell destruction contributes to the hyperbilirubinaemia during the neonatal period. He presents evidence that the foetal red cells do indeed have a lifespan that is slightly shorter than that of adult red cells, but also that the increase in serum bilirubin does not correspond to the fall in haemoglobin concentration. The short life-span of the foetal red cells may possibly, according to Vest, contribute to the anaemia of the first three months of life, but cannot account for the increase in serum bilirubin after birth. His interpretation seems reasonable, but is not conclusive, since it is based neither upon measurements of the changes in the total haemoglobin during the neonatal period nor upon reliable determinations of the survival-time of the red cells.

As a whole, Vest's work is interesting and well worth study. There is little that is actually new, but the investigations confirm earlier experience and the presentation is clear and up to date.

Stig Sjölin, Uppsala

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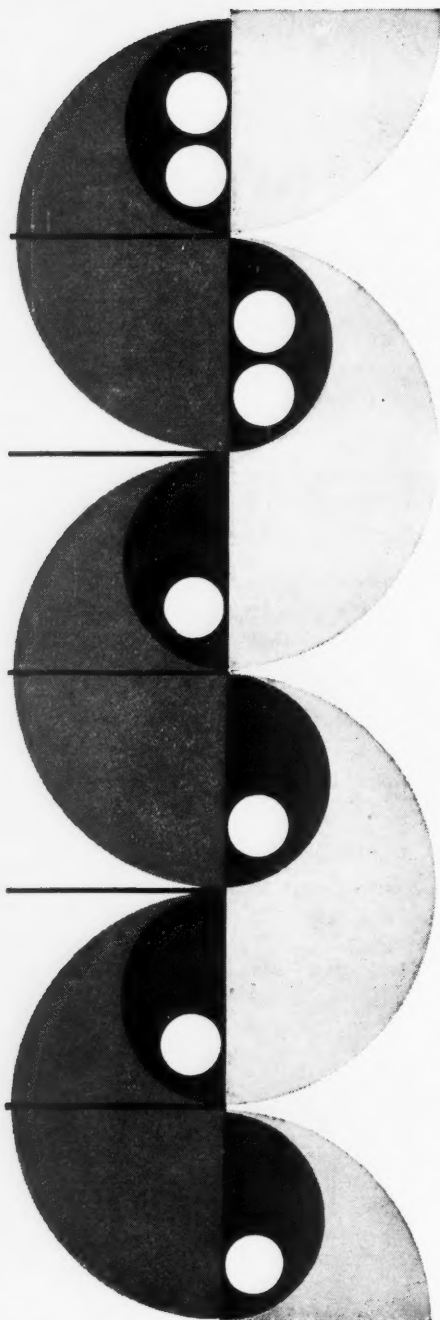
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